WHO monographs on selected medicinal plants

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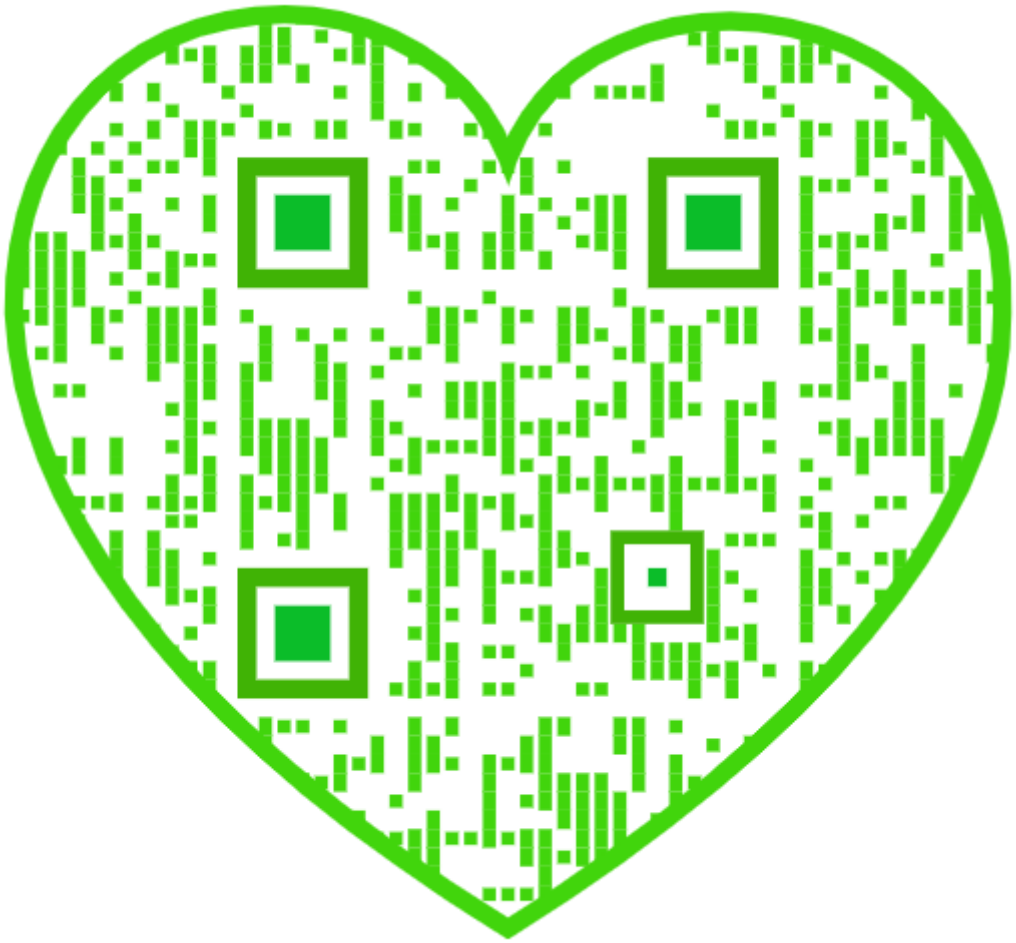

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Acknowledgements

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WHO also acknowledges with thanks the members of the advisory group that met in Beijing, China, in 1994, to draw up a list of medicinal plants for which monographs should be prepared, the more than 100 experts who provided comments and advice on the draft texts, and those who participated in the WHO Consultation held in Munich, Germany, in 1996 to review the monographs (see Annex). Finally, WHO would like to thank the Food and Agriculture Organization of the United Nations and the United Nations Industrial Development Organization for their contributions and all those who submitted comments through the World Self-Medication Industry, a nongovernmental organization in official relations with WHO.

Introduction

During the past decade, traditional systems of medicine have become a topic of global importance. Current estimates suggest that, in many developing countries, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet primary health care needs. Although modern medicine may be available in these countries, herbal medicines (phytomedicines) have often maintained popularity for historical and cultural reasons. Concurrently, many people in developed countries have begun to turn to alternative or complementary therapies, including medicinal herbs.

Few plant species that provide medicinal herbs have been scientifically evaluated for their possible medical application. Safety and efficacy data are available for even fewer plants, their extracts and active ingredients, and the preparations containing them. Furthermore, in most countries the herbal medicines market is poorly regulated, and herbal products are often neither registered nor controlled. Assurance of the safety, quality, and efficacy of medicinal plants and herbal products has now become a key issue in industrialized and in developing countries. Both the general consumer and health-care professionals need up-to-date, authoritative information on the safety and efficacy of medicinal plants.

During the fourth International Conference of Drug Regulatory Authorities (ICDRA) held in Tokyo in 1986, WHO was requested to compile a list of medicinal plants and to establish international specifications for the most widely used medicinal plants and simple preparations. Guidelines for the assessment of herbal medicines were subsequently prepared by WHO and adopted by the sixth ICDRA in Ottawa, Canada, in 1991.[1] As a result of ICDRA's recommendations and in response to requests from WHO's Member States for assistance in providing safe and effective herbal medicines for use in national health-care systems, WHO is now publishing this first volume of 28 monographs on selected medicinal plants; a second volume is in preparation.

Preparation of the monographs

The medicinal plants featured in this volume were selected by an advisory group in Beijing in 1994. The plants selected are widely used and important in

[1] Guidelines for the assessment of herbal medicines. In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Volume 1*. Geneva, World Health Organization, 1997:31–37.

all WHO regions, and for each sufficient scientific information seemed available to substantiate safety and efficacy. The monographs were drafted by the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, United States of America. The content was obtained by a systematic review of scientific literature from 1975 until the end of 1995: review articles; bibliographies in review articles; many pharmacopoeias—the International, African, British, Chinese, Dutch, European, French, German, Hungarian, Indian, and Japanese; as well as many other reference books.

Draft monographs were widely distributed, and some 100 experts in more than 40 countries commented on them. Experts included members of WHO's Expert Advisory Panels on Traditional Medicine, on the International Pharmacopoeia and Pharmaceutical Preparations, and on Drug Evaluation and National Drug Policies; and the drug regulatory authorities of 16 countries.

A WHO Consultation on Selected Medicinal Plants was held in Munich, Germany, in 1996. Sixteen experts and drug regulatory authorities from Member States participated. Following extensive discussion, 28 of 31 draft monographs were approved. The monograph on one medicinal plant was rejected because of the plant's potential toxicity. Two others will be reconsidered when more definitive data are available. At the subsequent eighth ICDRA in Bahrain later in 1996, the 28 model monographs were further reviewed and endorsed, and Member States requested WHO to prepare additional model monographs.

Purpose and content of the monographs

The purpose of the monographs is to:

- provide scientific information on the safety, efficacy, and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in Member States;
- provide models to assist Member States in developing their own monographs or formularies for these or other herbal medicines; and
- facilitate information exchange among Member States.

Readers will include members of regulatory authorities, practitioners of orthodox and of traditional medicine, pharmacists, other health professionals, manufacturers of herbal products, and research scientists.

Each monograph contains two parts. The first part consists of pharmacopoeial summaries for quality assurance: botanical features, distribution, identity tests, purity requirements, chemical assays, and active or major chemical constituents. The second part summarizes clinical applications, pharmacology, contraindications, warnings, precautions, potential adverse reactions, and posology.

In each pharmacopoeial summary, the *Definition* section provides the Latin binomial pharmacopoeial name, the most important criterion in quality assurance. Latin pharmacopoeial synonyms and vernacular names, listed in the

sections *Synonyms* and *Selected vernacular names*, are those names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Rules of Nomenclature.

For example, *Aloe barbadensis* Mill. is actually *Aloe vera* (L.) Burm. *Cassia acutifolia* Delile and *Cassia angustifolia* Vahl., often treated in separate monographs, are now believed to be the same species, *Cassia senna* L. *Matricaria chamomilla* L., *M. recutita* L., and *M. suaveolens* L. have been used for many years as the botanical name for camomile. However, it is now agreed that the name *Chamomilla recutita* (L.) Rauschert is the legitimate name.

The vernacular names listed are a selection of names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. The lists are not complete, but reflect the names appearing in the official monographs and reference books consulted during preparation of the WHO monographs and in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago).

A detailed botanical description (under *Description*) is intended for quality assurance at the stages of production and collection, whereas the detailed description of the drug material (under *Plant material of interest*) is for the same purpose at the manufacturing and commerce stages. *Geographical distribution* is not normally found in official compendia, but it is included here to provide additional quality assurance information.

General identity tests, *Purity tests*, and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with national requirements by the appropriate Member State authorities.

Each medicinal plant and the specific plant part used (the drug) contain active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the section *Major chemical constituents*.

The second part of each monograph begins with a list of *Dosage forms* and of *Medicinal uses* categorized as those uses supported by clinical data, those uses described in pharmacopoeias and in traditional systems of medicine, and those uses described in folk medicine, not yet supported by experimental or clinical data.

The first category includes medical indications that are well established in some countries and that have been validated by clinical studies documented in the world's scientific literature. The clinical trials may have been controlled, randomized, double-blind studies, open trials, or well-documented observations of therapeutic applications. Experts at the Munich Consultation agreed to include Folium and Fructus Sennae, Aloe, Rhizoma Rhei, and Herba Ephedrae

in this category because they are widely used and their efficacy is well documented in the standard medical literature.

The second category includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or national monographs. Well-established uses having a plausible pharmacological basis and supported by older studies that clearly need to be repeated are also included. The references cited provide additional information useful in evaluating specific herbal preparations. The uses described should be reviewed by local experts and health workers for their applicability in the local situation.

The third category refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. The appropriateness of these uses could not be assessed, owing to a lack of scientific data to support the claims. The possible use of these remedies must be carefully considered in the light of therapeutic alternatives.

The final sections of each monograph cover *Pharmacology* (both experimental and clinical); *Contraindications* such as sensitivity or allergy; *Warnings*; *Precautions*, including discussion of drug interactions, carcinogenicity, teratogenicity and special groups such as children and nursing mothers; *Adverse reactions*; and *Posology*.

Use of the monographs

WHO encourages countries to provide safe and effective traditional remedies and practices in public and private health services.

This publication is not intended to replace official compendia such as pharmacopoeias, formularies, or legislative documents. The monographs are intended primarily to promote harmonization in the use of herbal medicines with respect to levels of safety, efficacy, and quality control. These aspects of herbal medicines depend greatly on how the individual dosage form is prepared. For this reason, local regulatory authorities, experts, and health workers, as well as the scientific literature, should be consulted to determine whether a specific herbal preparation is appropriate for use in primary health care.

The monographs will be supplemented and updated periodically as new information appears in the literature, and additional monographs will be prepared. WHO would be pleased to receive comments and suggestions, to this end, from readers of the monographs.

Finally, I should like to express our appreciation of the support provided for the development of the monographs by Dr H. Nakajima and Dr F. S. Antezana during their time as Director-General and Assistant Director-General, respectively, of WHO.

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Bulbus Allii Cepae

Definition

Bulbus Allii Cepae is the fresh or dried bulbs of *Allium cepa* L. (Liliaceae) or its varieties and cultivars.

Synonyms

Allium esculentum Salisb., *Allium porrum cepa* Rehb. (*1*).

Selected vernacular names

It is most commonly known as "onion". Basal, basl, cebolla, cebolla morada, cepa bulb, cepolla, cipolla, common onion, cu hanh, hom hua yai, hom khaao, hom yai, hu-t'sung, hu t'sung t'song, hua phak bhu, i-i-bsel, kesounni, khtim, Küchenzwiebel, l'oignon, loyon, Madras oignon, oignon, palandu, piyaj, piyaz, pyaz, pyaaz, ralu lunu, red globe onion, sibuyas, Spanish onion, tamanegi, umbi bawang merah, vengayan, yellow Bermuda onion, white globe onion, Zwiebel (*1–5*).

Description

A perennial herb, strong smelling when crushed; bulbs vary in size and shape from cultivar to cultivar, often depressed-globose and up to 20 cm in diameter; outer tunics membranous. Stem up to 100 cm tall and 30 mm in diameter, tapering from inflated lower part. Leaves up to 40 cm in height and 20 mm in diameter, usually almost semicircular in section and slightly flattened on upper side; basal in first year, in second year their bases sheathing the lower sixth of the stem. Spathe often 3-valved, persistent, shorter than the umbel. Umbel 4–9 cm in diameter, subglobose or hemispherical, dense, many-flowered; pedicels up to 40 mm, almost equal. Perianth stellate; segments 3–4.5 × 2–2.5 mm, white, with green stripe, slightly unequal, the outer ovate, the inner oblong, obtuse or acute. Stamens exserted; filaments 4–5 mm, the outer subulate, the inner with an expanded base up to 2 mm wide and bearing short teeth on each side. Ovary whitish. Capsule about 5 mm, $2n = 16$ (*6*).

Plant material of interest: fresh or dried bulbs

General appearance

Macroscopically, Bulbus Allii Cepae varies in size and shape from cultivar to cultivar, 2–20 cm in diameter; flattened, spherical or pear-shaped; white or coloured (*7*).

Organoleptic properties

Odour strong, characteristic alliaceous; taste strong; crushing or cutting the bulb stimulates lachrymation.

Microscopic characteristics

The external dried leaf scales of the bulbs show a large-celled epidermis with lightly spotted cell walls; the cells are elongated longitudinally. The underlying hypodermis runs perpendicular to the epidermis and contains large calcium oxalate crystals bordering the cell walls. The epidermis of the fleshy leaf scales resembles that of the dried leaf scales, and the epidermal cells on the dorsal side are distinctly longer and more elongated than the epidermal cells on the ventral side. Large calcium oxalate crystals are found in the hypodermis; stomata rare; large cell nuclei conspicuous; and spiral vessel elements occur in the leaf mesophyll (*8*).

Powdered plant material

Contains mainly thin-walled cells of the mesophyll with broken pieces of spiral vessel elements; cells containing calcium oxalate crystals are scarce (*8*).

Geographical distribution

Bulbus Allii Cepae ("onion") is probably indigenous to western Asia, but it is commercially cultivated worldwide, especially in regions of moderate climate (*1*).

General identity tests

Macroscopic inspection, microscopic characteristics and microchemical examination for organic sulfur compounds (*9*); and thin-layer chromatographic analysis for the presence of cysteine sulfoxides (*10*, *11*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Bulbus Allii Cepae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*12*–*14*). Preparations for oral use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 6% (*3*).

Acid-insoluble ash

Not more than 1.0% (*3*).

Water-soluble extractive

Not more than 5.0% (*3*).

Alcohol-soluble extractive

Not more than 4.0% (*3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Bulbus Allii Cepae is not more than 0.05 mg/kg (*14*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*12*) and guidelines for predicting dietary intake of pesticide residues (*15*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*12*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137 and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*12*).

Other purity tests

Chemical, foreign organic matter, and moisture tests to be established in accordance with national requirements.

Chemical assays

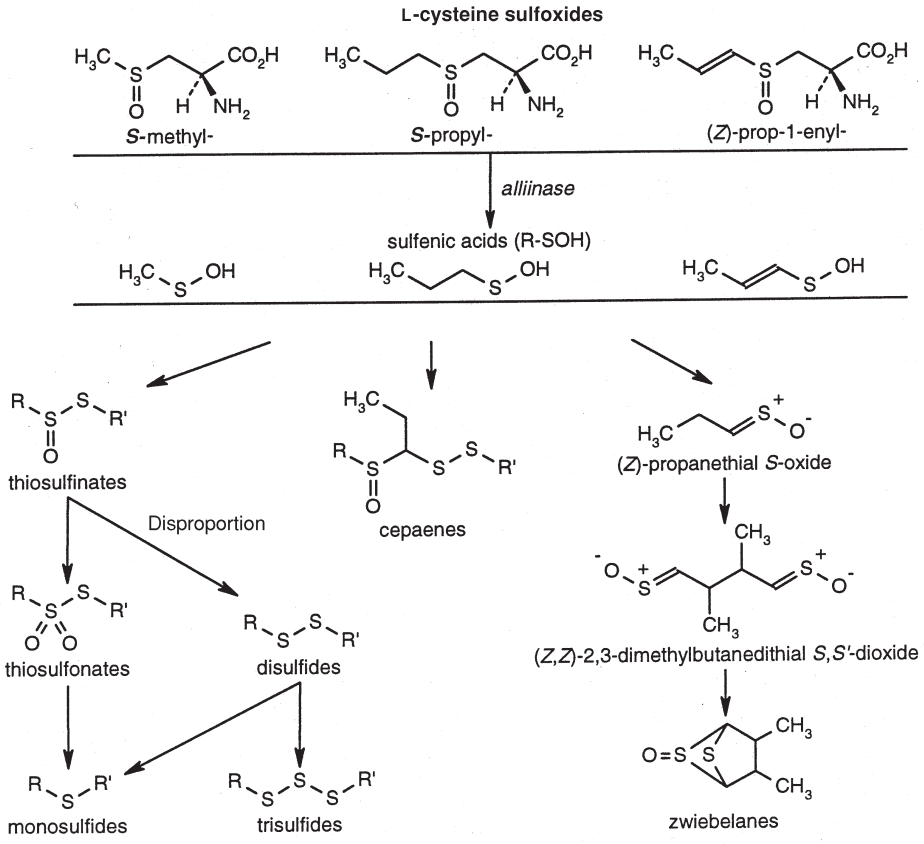
Assay for organic sulfur constituents, cysteine sulfoxides and sulfides by means of high-performance liquid chromatographic (*16*, *17*) or gas–liquid chromatographic (*18*) methods, respectively. Quantitative levels to be established by appropriate national authority.

Major chemical constituents

Sulfur- and non-sulfur-containing chemical constituents have been isolated from Bulbus Allii Cepae; the sulfur compounds are the most characteristic (*1*, *4*, *7*).

The organic sulfur compounds of Bulbus Allii Cepae, including the thiosulfinates, thiosulfonates, cepaenes, *S*-oxides, *S*,*S*′-dioxides, monosulfides,

disulfides, trisulfides, and zwiebelanes occur only as degradation products of the naturally occurring cysteine sulfoxides (e.g. (+)-*S*-propyl-L-cysteine sulfoxide). When the onion bulb is crushed, minced, or otherwise processed, the cysteine sulfoxides are released from compartments and contact the enzyme alliinase in adjacent vacuoles. Hydrolysis and immediate condensation of the reactive intermediate (sulfenic acids) form the compounds as indicated below (*1*). The odorous thiosulphonates occur (in low concentrations) only in freshly chopped onions, whereas the sulfides accumulate in stored extracts or steam-distilled oils. Approximately 90% of the soluble organic-bound sulfur is present as γ-glutamylcysteine peptides, which are not acted on by alliinase. They function as storage reserve and contribute to the germination of seeds. However, on prolonged storage or during germination, these peptides are acted on by γ-glutamyl transpeptidase to form alk(en)yl-cysteine sulfoxides, which in turn give rise to other volatile sulfur compounds (*1*).



Dosage forms

Fresh juice and 5% and 50% ethanol extracts have been used in clinical studies (*1*). A "soft" extract is marketed in France but is not recognized as a drug by French authorities (*7*). Dried Bulbus Allii Cepae products should be stored in well-closed containers, protected from light, moisture, and elevated temperature. Fresh bulbs and juice should be refrigerated (2–10 °C).

Medicinal uses

Uses supported by clinical data

The principal use of Bulbus Allii Cepae today is to prevent age-dependent changes in the blood vessels, and loss of appetite (*19*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of bacterial infections such as dysentery, and as a diuretic (*2*, *7*). The drug has also been used to treat ulcers, wounds, scars, keloids (*3*), and asthma (*20*, *21*). Bulbus Allii Cepae has also been used as an adjuvant therapy for diabetes (*4*, *22*, *23*).

Uses described in folk medicine, not supported by experimental or clinical data

As an anthelminthic, aphrodisiac, carminative, emmenagogue, expectorant, and tonic (*3*), and for the treatment of bruises, bronchitis, cholera, colic, earache, fevers, high blood pressure, jaundice, pimples, and sores (*3*).

Pharmacology

Experimental pharmacology

An aqueous extract or the juice of Bulbus Allii Cepae inhibited the *in vitro* growth of *Escherichia coli, Serratia marcescens, Streptococcus* species, *Lactobacillus odontolyticus, Pseudomonas aeruginosa*, and *Salmonella typhosa* (*24–28*). A petroleum ether extract of Bulbus Allii Cepae inhibited the *in vitro* growth of *Clostridium paraputrificum* and *Staphylococcus aureus* (*24*). The essential oil has activity against a variety of fungi including *Aspergillus niger*, *Cladosporium werneckii*, *Candida albicans*, *Fusarium oxysporium*, *Saccharomyces cerevisiae*, *Geotrichum candidum*, *Brettanomyces anomalus*, and *Candida lipolytica* (*5*, *29*).

The hypoglycaemic effects of Bulbus Allii Cepae have been demonstrated *in vivo*. Intragastric administration of the juice, a chloroform, ethanol, petroleum ether (0.25 g/kg) or water extract (0.5 ml), suppressed alloxan-, glucose- and epinephrine-induced hyperglycaemia in rabbits and mice (*30–35*).

Inhibition of platelet aggregation by Bulbus Allii Cepae has been demonstrated both *in vitro* and *in vivo*. An aqueous extract inhibited adenosine diphosphate-, collagen-, epinephrine- and arachidonic acid-induced platelet

aggregation *in vitro* (*36*, *37*). Platelet aggregation was inhibited in rabbits after administration of the essential oil, or a butanol or chloroform extract of the drug (*38–40*). An ethanol, butanol or chloroform extract or the essential oil (10–60 μg/ml) of the drug inhibited aggregation of human platelets *in vitro* (*41*, *42*) by decreasing thromboxane synthesis (*39*). Both raw onions and the essential oil increased fibrinolysis in *ex vivo* studies on rabbits and humans (*1*). An increase in coagulation time was also observed in rabbits (*1*).

Intragastric administration of the juice or an ether extract (100 mg/kg) of the drug inhibited allergen- and platelet activating factor-induced allergic reactions, but not histamine- or acetylcholine-induced allergenic responses in guinea-pigs (*43*). A water extract of the drug was not active (*43*). A chloroform extract of Bulbus Allii Cepae (20–80 mg/kg) inhibited allergen- and platelet aggregation factor-induced bronchial obstruction in guinea-pigs (*44*). The thiosulphinates and cepaenes appear to be the active constituents of Bulbus Allii Cepae (*1*).

Both ethanol and methanol extracts of Bulbus Allii Cepae demonstrated diuretic activity in dogs and rats after intragastric administration (*45*, *46*).

Antihyperlipidaemic and anticholesterolaemic activities of the drug were observed after oral administration of minced bulbs, a water extract, the essential oil (100 mg/kg), or the fixed oil to rabbits or rats (*47–52*). However, one study reported no significant changes in cholesterol or lipid levels of the eye in rabbits, after treatment of the animals for 6 months with an aqueous extract (20% of diet) (*53*).

Oral administration of an ethanol extract of the drug to guinea-pigs inhibited smooth muscle contractions in the trachea induced by carbachol and inhibited histamine-, barium chloride-, serotonin-, and acetylcholine-induced contractions in the ileum (*20*).

Topical application of an aqueous extract of Bulbus Allii Cepae (10% in a gel preparation) inhibited mouse ear oedema induced by arachidonic acid (*54*). The active antiallergic and anti-inflammatory constituents of onion are the flavonoids (quercetin and kaempferol) (*55*). The flavonoids act as anti-inflammatory agents because they inhibit the action of protein kinase, phospholipase A2, cyclooxygenase, and lipoxygenase (*56*), as well as the release of mediators of inflammation (e.g. histamine) from leukocytes (*57*).

In vitro, an aqueous extract of Bulbus Allii Cepae inhibited fibroblast proliferation (*58*). A 0.5% aqueous extract of onion inhibited the growth of human fibroblasts and of keloidal fibroblasts (enzymically isolated from keloidal tissue) (*59*). In a comparative study, an aqueous extract of Bulbus Allii Cepae (1–3%) inhibited the proliferation of fibroblasts of varying origin (scar, keloid, embryonic tissue). The strongest inhibition was observed with keloid fibroblasts (65–73%) as compared with the inhibition of scar and embryonic fibroblasts (up to 50%) (*59*). In human skin fibroblasts, both aqueous and chloroform onion extracts, as well as thiosulfinates, inhibited the platelet-derived growth factor-stimulated chemotaxis and proliferation of these cells (*60*). In addition, a protein fraction isolated from an onion extract exhibited antimitotic activity (*61*).

Clinical pharmacology

Oral administration of a butanol extract of Bulbus Allii Cepae (200 mg) to subjects given a high-fat meal prior to testing suppressed platelet aggregation associated with a high-fat diet (*62*).

Administration of a butanol extract to patients with alimentary lipaemia prevented an increase in the total serum cholesterol, β-lipoprotein cholesterol, and β-lipoprotein and serum triglycerides (*63*, *64*). A saponin fraction (50 mg) or the bulb (100 mg) also decreased serum cholesterol and plasma fibrinogen levels (*65*, *66*). However, fresh onion extract (50 g) did not produce any significant effects on serum cholesterol, fibrinogen, or fibrinolytic activity in normal subjects (*67*, *68*).

Antihyperglycaemic activity of Bulbus Allii Cepae has been demonstrated in clinical studies. Administration of an aqueous extract (100 mg) decreased glucose-induced hyperglycaemia in human adults (*69*). The juice of the drug (50 mg) administered orally to diabetic patients reduced blood glucose levels (*22*). Addition of raw onion to the diet of non-insulin-dependent diabetic subjects decreased the dose of antidiabetic medication required to control the disease (*70*). However, an aqueous extract of Bulbus Allii Cepae (200 mg) was not active (*71*).

The immediate and late cutaneous reactions induced by injection of rabbit anti-human IgE-antibodies into the volar side of the forearms of 12 healthy volunteers were reduced after pretreatment of the skin with a 50% ethanol onion extract (*1*). Immediate and late bronchial obstruction owing to allergen inhalation was markedly reduced after oral administration of a 5% ethanol onion extract 1 hour before exposure to the allergen (*1*).

In one clinical trial in 12 adult subjects, topical application of a 45% ethanolic onion extract inhibited the allergic skin reactions induced by anti-IgE (*72*).

Contraindications

Allergies to the plant. The level of safety of Bulbus Allii Cepae is reflected by its worldwide use as a vegetable.

Warnings

No warnings have been reported.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Bulbus Allii Cepae is not mutagenic *in vitro* (*73*).

Other precautions

No general precautions have been reported, and no precautions have been reported concerning drug interactions, drug and laboratory test interactions,

nursing mothers, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

Allergic reactions such as rhinoconjunctivitis and contact dermatitis have been reported (*74*).

Posology

Unless otherwise prescribed: a daily dosage is 50 g of fresh onion or 20 g of the dried drug; doses of preparations should be calculated accordingly (*14*).

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Bulbus Allii Sativi

Definition

Bulbus Allii Sativi consists of the fresh or dried bulbs of *Allium sativum* L. (Liliaceae) (*1*, *2*).

Synonyms

Porvium sativum Rehb. (*1*, *3*).

Selected vernacular names

It is most commonly known as "garlic". Ail, ail commun, ajo, akashneem, allium, alubosa elewe, ayo-ishi, ayu, banlasun, camphor of the poor, dai tóan, dasuan, dawang, dra thiam, foom, Gartenlauch, hom khaao, hom kía, hom thiam, hua thiam, kesumphin, kitunguu-sumu, Knoblauch, kra thiam, krathiam, krathiam cheen, krathiam khaao, l'ail, lahsun, lai, lashun, lasan, lasun, lasuna, Lauch, lay, layi, lehsun, lesun, lobha, majo, naharu, nectar of the gods, ninniku, pa-se-waa, poor man's treacle, rason, rasonam, rasun, rustic treacles, seer, skordo, sluôn, stinking rose, sudulunu, ta-suam, ta-suan, tafanuwa, tellagada, tellagaddalu, thiam, toi thum, tum, umbi bawang putih, vallaippundu, velluli, vellulli (*1*–*13*).

Description

A perennial, erect bulbous herb, 30–60 cm tall, strong smelling when crushed. The underground portion consists of a compound bulb with numerous fibrous rootlets; the bulb gives rise above ground to a number of narrow, keeled, grass-like leaves. The leaf blade is linear, flat, solid, 1.0–2.5 cm wide, 30–60 cm long, and has an acute apex. Leaf sheaths form a pseudostem. Inflorescences are umbellate; scape smooth, round, solid, and coiled at first, subtended by membraneous, long-beaked spathe, splitting on one side and remaining attached to umbel. Small bulbils are produced in inflorescences; flowers are variable in number and sometimes absent, seldom open and may wither in bud. Flowers are on slender pedicels; consisting of perianth of 6 segments, about 4–6 mm long, pinkish; stamens 6, anthers exserted; ovary superior, 3-locular. Fruit is a small loculicidal capsule. Seeds are seldom if ever produced (*8*, *9*).

Plant material of interest: fresh or dried bulbs

General appearance

Bulbus Allii Sativi consists of several outer layers of thin sheathing protective leaves which surround an inner sheath. The latter enclose the swollen storage leaves called "cloves". Typically, the bulb possesses a dozen sterile sheathing leaves within which are 6–8 cloves bearing buds making a total of 10–20 cloves and 20–40 well-developed but short and embedded roots. The cloves are asymmetric in shape, except for those near the centre (*1*).

Organoleptic properties

Odour strong, characteristic alliaceous (*1*, *6*, *8*); taste very persistently pungent and acrid (*1*, *6*, *8*).

Microscopic characteristics

The bulbs show a number of concentric bulblets; each is 5–10 mm in diameter and consists of an outer scale, an epidermis enclosing a mesophyll free from chlorophyll, a ground tissue and a layer of lower epidermal cells. Dry scales consist of 2 or 3 layers of rectangular cells having end walls with a broadly angular slant. These cells contain many rhomboid crystals of calcium oxalate. The upper epidermal cells next to the dry scale layer consist of a single layer of rectangular to cubical cells next to which are several layers of large parenchymatous cells. Among these cells are interspaced many vascular bundles, each of which consists of xylem and phloem arranged alternately. Lower epidermis consists of cubical cells which are much smaller than the upper epidermal cells. The same arrangement of tissues is met within different bulblets, 2 or 3 of which are arranged concentrically (*1*, *6*).

Powdered plant material

Pale buff to greyish or purplish white, with characteristic aromatic alliaceous odour and taste. It is characterized by the presence of sclereids of the epidermis of protective leaves, thin epidermis of storage cells, latex tubes, swollen parenchyma cells with granular contents, and lignified narrow spiral and annular vessels (*1*).

Geographical distribution

Bulbus Allii Sativi is probably indigenous to Asia (*1*, *7*), but it is commercially cultivated in most countries.

General identity tests

Macroscopic and microscopic examinations and microchemical analysis are used to identify organic sulfur compounds (*1*), thin-layer chromatographic analysis to determine the presence of alliin (*14*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Bulbus Allii Sativi products should be negative. The maximum acceptable limits of other microorganisms are as follows (*2*, *15*, *16*). Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 5.0% (*2*).

Acid-insoluble ash

Not more than 1.0% (*4*).

Water-soluble extractive

Not less than 5.0% (*4*).

Alcohol-soluble extractive

Not less than 4.0% (*4*).

Moisture

Not more than 7% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Bulbus Allii Sativi is not more than 0.05 mg/kg (*2*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residues (*17*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

Chemical tests and tests for foreign organic matter to be established in accordance with national requirements.

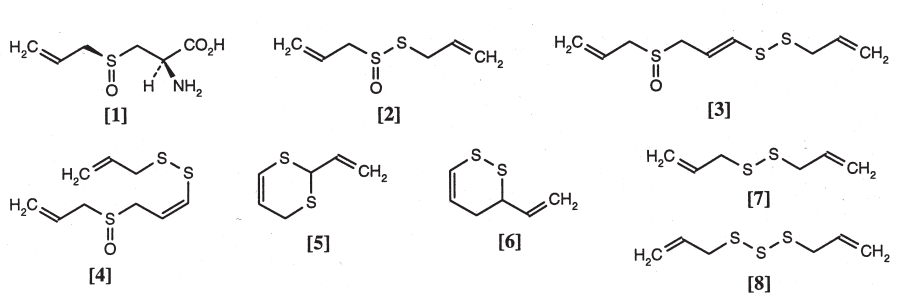
Chemical assays

Qualitative and quantitative assay for sulfur constituents (alliin, allicin etc.) content by means of high-performance liquid chromatography (*18–22*) or gas chromatography–mass spectroscopy (*23*) methods.

Major chemical constituents

The most important chemical constituents reported from Bulbus Allii Sativi are the sulfur compounds (*7*, *9*, *24*, *25*). It has been estimated that cysteine sulfoxides (e.g. alliin [**1**]) and the non-volatile γ-glutamylcysteine peptides make up more than 82% of the total sulfur content of garlic (*25*).

The thiosulfinates (e.g. allicin [**2**]), ajoenes (e.g. *E*-ajoene [**3**], *Z*-ajoene [**4**]), vinyldithiins (e.g. 2-vinyl-(4*H*)-1,3-dithiin [**5**], 3-vinyl-(4*H*)-1,2-dithiin [**6**]), and sulfides (e.g. diallyl disulfide [**7**], diallyl trisulfide [**8**]), however, are not naturally occurring compounds. Rather, they are degradation products from the naturally occurring cysteine sulfoxide, alliin [**1**]. When the garlic bulb is crushed, minced, or otherwise processed, alliin is released from compartments and interacts with the enzyme alliinase in adjacent vacuoles. Hydrolysis and immediate condensation of the reactive intermediate (allylsulfenic acid) forms allicin [**2**]. One milligram of alliin is considered to be equivalent to 0.45 mg of allicin (*26*). Allicin itself is an unstable product and will undergo additional reactions to form other derivatives (e.g. products [**3**]–[**8**]), depending on environmental and processing conditions (*24–26*). Extraction of garlic cloves with ethanol at <0 °C gave alliin [**1**]; extraction with ethanol and water at 25 °C led to allicin [**2**] and no alliin; and steam distillation (100 °C) converted the alliin totally to diallyl sulfides [**7**], [**8**] (*24*, *25*). Sulfur chemical profiles of Bulbus Allii Sativi products reflected the processing procedure: bulb, mainly alliin, allicin; dry powder, mainly alliin, allicin; volatile oil, almost entirely diallyl sulfide, diallyl disulfide, diallyl trisulfide, and diallyl tetrasulfide; oil macerate, mainly 2-vinyl-[4*H*]-1,3-dithiin, 3-vinyl-[4*H*]-1,3-dithiin, *E*-ajoene, and *Z*-ajoene (*18–22*, *24*). The content of alliin



was also affected by processing treatment: whole garlic cloves (fresh) contained 0.25–1.15% alliin, while material carefully dried under mild conditions contained 0.7–1.7% alliin (*18–21*).

Gamma-glutamylcysteine peptides are not acted on by alliinase. On prolonged storage or during germination, these peptides are acted on by γ-glutamyl transpeptidase to form thiosulfinates (*25*).

Dosage forms

Fresh bulbs, dried powder, volatile oil, oil macerates, juice, aqueous or alcoholic extracts, aged garlic extracts (minced garlic that is incubated in aqueous alcohol (15–20%) for 20 months, then concentrated), and odourless garlic products (garlic products in which the alliinase has been inactivated by cooking; or in which chlorophyll has been added as a deodorant; or aged garlic preparations that have low concentrations of water-soluble sulfur compounds) (*18, 24*).

The juice is the most unstable dosage form. Alliin and allicin decompose rapidly, and those products must be used promptly (*18*).

Dried Bulbus Allii Sativi products should be stored in well-closed containers, protected from light, moisture, and elevated temperature.

Medicinal uses

Uses supported by clinical data

As an adjuvant to dietetic management in the treatment of hyperlipidaemia, and in the prevention of atherosclerotic (age-dependent) vascular changes (*5, 27–31*). The drug may be useful in the treatment of mild hypertension (*11, 28*).

Uses described in pharmacopoeias and in traditional systems of medicine

The treatment of respiratory and urinary tract infections, ringworm and rheumatic conditions (*1, 4, 7, 9, 11*). The herb has been used as a carminative in the treatment of dyspepsia (*32*).

Uses described in folk medicine, not supported by experimental or clinical data

As an aphrodisiac, antipyretic, diuretic, emmenagogue, expectorant, and sedative, to treat asthma and bronchitis, and to promote hair growth (*6, 9, 13*).

Pharmacology

Experimental pharmacology

Bulbus Allii Sativi has a broad range of antibacterial and antifungal activity (*13*). The essential oil, water, and ethanol extracts, and the juice inhibit the *in vitro* growth of *Bacillus* species, *Staphylococcus aureus*, *Shigella sonnei*, *Erwinia carotovora*, *Mycobacterium tuberculosis*, *Escherichia coli*, *Pasteurella multocida*, *Proteus*

species, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Candida* species, *Cryptococcus* species, *Rhodotorula rubra*, *Toruloposis* species, *Trichosporon pullulans*, and *Aspergillus niger* (*33–40*). Its antimicrobial activity has been attributed to allicin, one of the active constituents of the drug (*41*). However, allicin is a relatively unstable and highly reactive compound (*37*, *42*) and may not have antibacterial activity *in vivo*. Ajoene and diallyl trisulfide also have antibacterial and antifungal activities (*43*). Garlic has been used in the treatment of roundworm (*Ascaris strongyloides*) and hookworm (*Ancylostoma caninum* and *Necator americanus*) (*44*, *45*). Allicin appears to be the active anthelminthic constituent, and diallyl disulfide was not effective (*46*).

Fresh garlic, garlic juice, aged garlic extracts, or the volatile oil all lowered cholesterol and plasma lipids, lipid metabolism, and atherogenesis both *in vitro* and *in vivo* (*18*, *43*, *47–64*). *In vitro* studies with isolated primary rat hepatocytes and human HepG2 cells have shown that water-soluble garlic extracts inhibited cholesterol biosynthesis in a dose-dependent manner (*48–50*). Antihypercholesterolaemic and antihyperlipidaemic effects were observed in various animal models (rat, rabbit, chicken, pig) after oral (in feed) or intragastric administration of minced garlic bulbs; water, ethanol, petroleum ether, or methanol extracts; the essential oil; aged garlic extracts and the fixed oil (*51–64*). Oral administration of allicin to rats during a 2-month period lowered serum and liver levels of total lipids, phospholipids, triglycerides, and total cholesterol (*65*). Total plasma lipids and cholesterol in rats were reduced after intraperitoneal injection of a mixture of diallyl disulfide and diallyl trisulfide (*66*). The mechanism of garlic's antihypercholesterolaemic and antihyperlipidaemic activity appears to involve the inhibition of hepatic hydroxymethylglutaryl-CoA (HMG-CoA) reductase and remodelling of plasma lipoproteins and cell membranes (*67*). At low concentrations (<0.5 mg/ml), garlic extracts inhibited the activity of hepatic HMG-CoA reductase, but at higher concentrations (>0.5 mg/ml) cholesterol biosynthesis was inhibited in the later stages of the biosynthetic pathway (*68*). Alliin was not effective, but allicin and ajoene both inhibited HMG-CoA reductase *in vitro* (IC_{50} = 7 and 9 mmol/l respectively) (*49*). Because both allicin and ajoene are converted to allyl mercaptan in the blood and never reach the liver to affect cholesterol biosynthesis, this mechanism may not be applicable *in vivo*. In addition to allicin and ajoene, allyl mercaptan (50 mmol/l) and diallyl disulfide (5 mmol/l) enhanced palmitate-induced inhibition of cholesterol biosynthesis *in vitro* (*50*). It should be noted that water extracts of garlic probably do not contain any of these compounds; therefore other constituents of garlic, such as nicotinic acid and adenosine, which also inhibit HMG-CoA reductase activity and cholesterol biosynthesis, may be involved (*69*, *70*).

The antihypertensive activity of garlic has been demonstrated *in vivo*. Oral or intragastric administration of minced garlic bulbs, or alcohol or water extracts of the drug, lowered blood pressure in dogs, guinea-pigs, rabbits, and rats (*52*, *71–73*). The drug appeared to decrease vascular resistance by directly relaxing smooth muscle (*74*). The drug appears to change the physical state functions of

the membrane potentials of vascular smooth muscle cells. Both aqueous garlic and ajoene induced membrane hyperpolarization in the cells of isolated vessel strips. The potassium channels opened frequently causing hyperpolarization, which resulted in vasodilation because the calcium channels were closed (*75*, *76*). The compounds that produce the hypotensive activity of the drug are uncertain. Allicin does not appear to be involved (*43*), and adenosine has been postulated as being associated with the activity of the drug. Adenosine enlarges the peripheral blood vessels, allowing the blood pressure to decrease, and is also involved in the regulation of blood flow in the coronary arteries; however, adenosine is not active when administered orally. Bulbus Allii Sativi may increase production of nitric oxide, which is associated with a decrease in blood pressure. *In vitro* studies using water or alcohol extracts of garlic or garlic powder activated nitric-oxide synthase (*77*), and these results have been confirmed by *in vivo* studies (*78*).

Aqueous garlic extracts and garlic oil have been shown *in vivo* to alter the plasma fibrinogen level, coagulation time, and fibrinolytic activity (*43*). Serum fibrinolytic activity increased after administration of dry garlic or garlic extracts to animals that were artificially rendered arteriosclerotic (*79*, *80*). Although adenosine was thought to be the active constituent, it did not affect whole blood (*43*).

Garlic inhibited platelet aggregation in both *in vitro* and *in vivo* studies. A water, chloroform, or methanol extract of the drug inhibited collagen-, ADP-, arachidonic acid-, epinephrine-, and thrombin-induced platelet aggregation *in vitro* (*81–87*). Prolonged administration (intragastric, 3 months) of the essential oil or a chloroform extract of Bulbus Allii Sativi inhibited platelet aggregation in rabbits (*88–90*). Adenosine, alliin, allicin, and the transformation products of allicin, the ajoenes; the vinyldithiins; and the dialkyloligosulfides are responsible for inhibition of platelet adhesion and aggregation (*4*, *42*, *91–93*). In addition methyl allyl trisulfide, a minor constituent of garlic oil, inhibited platelet aggregation at least 10 times as effectively than allicin (*94*). Inhibition of the arachidonic acid cascade appears to be one of the mechanisms by which the various constituents and their metabolites affect platelet aggregation. Inhibition of platelet cyclic AMP phosphodiesterase may also be involved (*91*).

Ajoene, one of the transformation products of allicin, inhibited *in vitro* platelet aggregation induced by the platelet stimulators—ADP, arachidonic acid, calcium ionophore A23187, collagen, epinephrine, platelet activating factor, and thrombin (*95*, *96*). Ajoene inhibited platelet aggregation in cows, dogs, guinea-pigs, horses, monkeys, pigs, rabbits, and rats (*95*, *96*). The antiplatelet activity of ajoene is potentiated by prostacyclin, forskolin, indometacin, and dipyridamole (*95*). The mechanism of action involves the inhibition of the metabolism of arachidonic acid by both cyclooxygenase and lipoxygenase, thereby inhibiting the formation of thromboxane A2 and 12-hydroxyeicosatetraenoic acid (*95*). Two mechanisms have been suggested for ajoene's antiplatelet activity. First, ajoene may interact with the primary agonist–receptor complex with the exposure of fibrinogen receptors through

specific G-proteins involved in the signal transduction system on the platelet membrane (*92*). Or it may interact with a haemoprotein involved in platelet activation that modifies the binding of the protein to its ligands (*96*).

Hypoglycaemic effects of Bulbus Allii Sativi have been demonstrated *in vivo*. Oral administration of an aqueous, ethanol, petroleum ether, or chloroform extract, or the essential oil of garlic, lowered blood glucose levels in rabbits and rats (*24*, *97–104*). However, three similar studies reported negative results (*105–107*). In one study, garlic bulbs administered orally (in feed) to normal or streptozotocin-diabetic mice reduced hyperphagia and polydipsia but had no effect on hyperglycaemia or hypoinsulinaemia (*107*). Allicin administered orally to alloxan-diabetic rats lowered blood glucose levels and increased insulin activity in a dose-dependent manner (*24*). Garlic extract's hypoglycaemic action appears to enhance insulin production, and allicin has been shown to protect insulin against inactivation (*108*).

Intragastric administration of an ethanol extract of Bulbus Allii Sativi decreased carrageenin-induced rat paw oedema at a dose of 100 mg/kg. The anti-inflammatory activity of the drug appears to be due to its antiprostaglandin activity (*109*, *110*).

A water or ethanol extract of the drug showed antispasmodic activity against acetylcholine, prostaglandin E2 and barium-induced contractions in guinea-pig small intestine and rat stomach (*111*). The juice of the drug relaxed smooth muscle of guinea-pig ileum, rabbit heart and jejunum, and rat colon and fundus (*112*, *113*). The juice also inhibited norepinephrine-, acetylcholine- and histamine-induced contractions in guinea-pig and rat aorta, and in rabbit trachea (*112*, *113*).

Clinical pharmacology

The efficacy of Bulbus Allii Sativi as a carminative has been demonstrated in human studies. A clinical study of 29 patients taking two tablets daily (~1000 mg/day) of a dried garlic preparation demonstrated that garlic relieved epigastric and abdominal distress, belching, flatulence, colic, and nausea, as compared with placebo (*32*). It was concluded that garlic sedated the stomach and intestines, and relaxed spasms, retarded hyperperistalsis, and dispersed gas (*32*).

A meta-analysis of the effect of Bulbus Allii Sativi on blood pressure reviewed a total of 11 randomized, controlled trials (published and unpublished) (*113*, *114*). Each of the trials used dried garlic powder (tablets) at a dose of 600–900 mg daily (equivalent to 1.8–2.7 g/day fresh garlic). The median duration of the trials was 12 weeks. Eight of the trials with data from 415 subjects were included in the analysis; three trials were excluded owing to a lack of data. Only three of the trials specifically used hypertensive subjects, and many of the studies suffered from methodological flaws. Of the seven studies that compared garlic with placebo, three reported a decrease in systolic blood pressure, and four studies reported a decrease in diastolic blood pressure (*115*). The results of

the meta-analysis led to the conclusion that garlic may have some clinical usefulness in mild hypertension, but there is still insufficient evidence to recommend the drug as a routine clinical therapy for the treatment of hypertension (*115*).

A meta-analysis of the effects of Bulbus Allii Sativi on serum lipids and lipoproteins reviewed 25 randomized, controlled trials (published and unpublished) (*116*) and selected 16 with data from 952 subjects to include in the analysis. Fourteen of the trials used a parallel group design, and the remaining two were cross-over studies. Two of the studies were conducted in an open-label fashion, two others were single-blind, and the remainder were double-blind. The total daily dose of garlic was 600–900 mg of dried garlic powder, or 10 g of raw garlic, or 18 mg of garlic oil, or aged garlic extracts (dosage not stated). The median duration of the therapy was 12 weeks. Overall, the subjects receiving garlic supplementation (powder or non-powder) showed a 12% reduction (average) in total cholesterol, and a 13% reduction (powder only) in serum triglycerides. Meta-analysis of the clinical studies confirmed the lipid-lowering action of garlic. However, the authors concluded that the overall quality of the clinical trials was poor and that favourable results of better-designed clinical studies should be available before garlic can be routinely recommended as a lipid-lowering agent. However, current available data support the hypothesis that garlic therapy is at least beneficial (*116*). Another meta-analysis of the controlled trials of garlic effects on total serum cholesterol reached similar conclusions (*117*). A systematic review of the lipid-lowering potential of a dried garlic powder preparation in eight studies with 500 subjects had similar findings (*118*). In seven of the eight studies reviewed, a daily dose of 600–900 mg of garlic powder reduced serum cholesterol and triglyceride levels by 5–20%. The review concluded that garlic powder preparations do have lipid-lowering potential (*118*).

An increase in fibrinolytic activity in the serum of patients suffering from atherosclerosis was observed after administration of aqueous garlic extracts, the essential oil, and garlic powder (*119*, *120*). Clinical studies have demonstrated that garlic activates endogenous fibrinolysis, that the effect is detectable for several hours after administration of the drug, and that the effect increases as the drug is taken regularly for several months (*43*, *121*). Investigations of the acute haemorheological (blood flow) effect of 600–1200 mg of dry garlic powder demonstrated that the drug decreased plasma viscosity, tissue plasminogen activator activity and the haematocrit level (*118*).

The effects of the drug on haemorheology in conjunctival vessels was determined in a randomized, placebo-controlled, double-blind, cross-over trial. Garlic powder (900 mg) significantly increased the mean diameter of the arterioles (by 4.2%) and venules (by 5.9%) as compared with controls (*122*). In another double-blind, placebo-controlled study, patients with stage II peripheral arterial occlusive disease were given a daily dose of 800 mg of garlic powder for 4 weeks (*123*, *124*). Increased capillary erythrocyte flow rate and decreased plasma viscosity and plasma fibrinogen levels were observed in the group

treated with the drug (*123*, *124*). Determinations of platelet aggregation *ex vivo*, after ingestion of garlic and garlic preparations by humans, suffers from methodological difficulties that may account for the negative results in some studies (*24*). In one study in patients with hypercholesterolinaemia treated with a garlic–oil macerate for 3 months, platelet adhesion and aggregation decreased significantly (*125*). In a 3-year intervention study, 432 patients with myocardial infarction were treated with either an ether-extracted garlic oil (0.1 mg/kg/day, corresponding to 2 g fresh garlic daily) or a placebo (*126*). In the group treated with garlic, there were 35% fewer new heart attacks and 45% fewer deaths than in the control group. The serum lipid concentrations of the treated patients were also reduced (*126*).

The acute and chronic effects of garlic on fibrinolysis and platelet aggregation in 12 healthy patients in a randomized, double-blind, placebo-controlled cross-over study were investigated (*30*). A daily dose of 900 mg of garlic powder for 14 days significantly increased tissue plasminogen activator activity as compared with placebo (*30*). Furthermore, platelet aggregation induced by adenosine diphosphate and collagen was significantly inhibited 2 and 4 hours after garlic ingestion and remained lower for 7 to 14 days after treatment (*30*). Another randomized, double-blind, placebo-controlled study investigated the effects of garlic on platelet aggregation in 60 subjects with increased risk of juvenile ischaemic attack (*29*). Daily ingestion of 800 mg of powdered garlic for 4 weeks significantly decreased the percentage of circulating platelet aggregates and spontaneous platelet aggregation as compared with the placebo group (*29*).

Oral administration of garlic powder (800 mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6% (*30*). Another study found no such activity after dosing non-insulin-dependent patients with 700 mg/day of a spray-dried garlic preparation for 1 month (*127*).

Contraindications

Bulbus Allii Sativi is contraindicated in patients with a known allergy to the drug. The level of safety for Bulbus Allii Sativi is reflected by its worldwide use as a seasoning in food.

Warnings

Consumption of large amounts of garlic may increase the risk of postoperative bleeding (*128*, *129*).

Precautions

Drug interactions

Patients on warfarin therapy should be warned that garlic supplements may increase bleeding times. Blood clotting times have been reported to double in patients taking warfarin and garlic supplements (*130*).

Carcinogenesis, mutagenesis, impairment of fertility

Bulbus Allii Sativi is not mutagenic *in vitro* (*Salmonella* microsome reversion assay and *Escherichia coli*) (*131*, *132*).

Pregnancy: non-teratogenic effects

There are no objections to the use of Bulbus Allii Sativi during pregnancy and lactation.

Nursing mothers

Excretion of the components of Bulbus Allii Sativi into breast milk and its effect on the newborn has not been established.

Other precautions

No general precautions have been reported, and no precautions have been reported concerning drug and laboratory test interactions, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

Bulbus Allii Sativi has been reported to evoke occasional allergic reactions such as contact dermatitis and asthmatic attacks after inhalation of the powdered drug (*133*). Those sensitive to garlic may also have a reaction to onion or tulip (*133*). Ingestion of fresh garlic bulbs, extracts, or oil on an empty stomach may occasionally cause heartburn, nausea, vomiting, and diarrhoea. Garlic odour from breath and skin may be perceptible (*7*). One case of spontaneous spinal epidural haematoma, which was associated with excessive ingestion of fresh garlic cloves, has been reported (*134*).

Posology

Unless otherwise prescribed, average daily dose is as follows (*7*): fresh garlic, 2–5 g; dried powder, 0.4–1.2 g; oil, 2–5 mg; extract, 300–1000 mg (as solid material). Other preparations should correspond to 4–12 mg of alliin or about 2–5 mg of allicin).

Bulbus Allii Sativi should be taken with food to prevent gastrointestinal upset.

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Aloe

Definition

Aloe is the dried juice of the leaves of *Aloe vera* (L.) Burm. f. or of *A. ferox* Mill. and its hybrids with *A. africana* Mill. and *A. spicata* Baker (Liliaceae) (*1–6*).

Synonyms

Aloe vera (L.) Burm. f.

Aloe barbadensis Mill., *Aloe chinensis* Bak., *A. elongata* Murray, *A. indica* Royle, *A. officinalis* Forsk., *A. perfoliata* L., *A. rubescens* DC, *A. vera* L. var. *littoralis* König ex Bak., *A. vera* L. var. *chinensis* Berger, *A. vulgaris* Lam. (*7*).

In most formularies and reference books, *Aloe barbadensis* Mill. is regarded as the correct species name, and *Aloe vera* (L.) Burm. f. is considered a synonym. However, according to the International Rules of Botanical Nomenclature, *Aloe vera* (L.) Burm. f. is the legitimate name for this species (*8–10*). The genus *Aloe* has also been placed taxonomically in a family called Aloeaceae.

Aloe ferox Mill.

Aloe horrida Haw., *A. perfoliata* Thunberg., *A. pseudoferox* Salm. Dyck, *A. socotrina* Masson., *A. supralaevis* Haw., *Pachydendron ferox* Humb. & Bonpl., *P. supralaeve* Haw. (*7*).

Selected vernacular names

Aloe capensis, aloe curacao, aloe vera, aloes, aloès, aloès du Cape, aloès fèroce, aloes vrai, aloès vulgaire, alovis, Barbadoes aloe, Barbadoes aloes, Barbados aloe, Bergaalwyn, Bitteraalwyn, Cape aloe, chirukattali, Curacao aloe, Curacao aloes, Curacao alos, Echte Aloe, ghai kunwar, ghai kunwrar, gheekuar, ghikanvar, ghikuar, ghikumar, ghikumari, ghikwar, ghiu kumari, ghrita kumari, ghritakumari, grahakanya, gwar-patha, haang takhe, hlaba, Indian aloe, jadam, korphad, kumari, kumaro, kunvar pata, kunwar, laloi, laluwe, lo-hoei, lo-hoi, lou-houey, lu wei, luchuy, manjikattali, Mediterranean aloe, murr sbarr, musabar, rokai, sabbara, saber, sábila, sabilla, sabr, saibr, savila, savilla, semper vivum, shubiri, sibr, siang-tan, star cactus, tuna, umhlaba, waan haang charakhe, wan-hangchorakhe, yaa dam, yadam, zábila, zambila (*1, 7, 11*).

Description

Aloe vera (L.) Burm. f.

Succulent, almost sessile perennial herb; leaves 30–50 cm long and 10 cm broad at the base; colour pea-green (when young spotted with white); bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike; stamens frequently project beyond the perianth tube (*12*).

Aloe ferox Mill.

Arborescent perennial shrub with a single stem of 2–3 m in height, crowned by a large rosette of numerous leaves which are glaucous, oval-lanceolate, 40–60 cm in length, thorny on the ridge and the edges; inflorescence an erect raceme 60 cm in height; flowers with perianth 2.5 cm in length, red, yellow, or orange (*2*).

Plant material of interest: dried juice

Solidified juice originating in the cells of the pericycle and adjacent leaf parenchyma, and flowing spontaneously from the cut leaf, allowed to dry with or without the aid of heat.

It is not to be confused with Aloe Vera Gel, which is the colourless mucilaginous gel obtained from the parenchymatous cells in the leaves of *Aloe vera* (L.) Burm. f. (*13*).

General appearance

Curacao or Barbados Aloe, derived from *Aloe vera* (L.) Burm. f.

The dried juice occurs in dark chocolate-brown usually opaque masses; fracture, dull waxy, uneven, and frequently conchoidal (*2*, *6*).

Cape Aloe, derived from *A. ferox* Mill. and its hybrids with *A. africana* Mill. and *A. spicata* Baker

The dried juice occurs in dark brown or greenish brown glassy masses, often covered with a yellowish powder; in thin fragments it is transparent and exhibits a yellowish, reddish brown or greenish tinge; fracture, smooth, even, and glassy (*2*, *6*).

Organoleptic properties

Aloe is marketed as opaque masses that range from reddish black to brownish black to dark brown in colour. Odour, characteristic and disagreeable; taste, somewhat sour, nauseating and very bitter (*2*, *7*, *12*).

Microscopic characteristics

See "Powdered plant material" below.

Powdered plant material

Powdered aloes are yellowish brown to dark reddish brown. Microscopically, Cape Aloe appears as transparent brown or greenish brown irregular and angular fragments; Curacao Aloe shows fragments with numerous minute acicular crystals embedded in an amorphous matrix (*1–3, 12, 14*).

Geographical distribution

Native to southern and eastern Africa, and subsequently introduced into northern Africa, the Arabian peninsula, China, Gibraltar, the Mediterranean countries, and the West Indies (*15*). It is commercially cultivated in Aruba, Bonaire, Haiti, India, South Africa, the United States of America, and Venezuela (*2, 7, 12, 14, 15*).

General identity tests

Macroscopic and microscopic examinations (*1–3, 7, 12, 14*); solvent solubility (hot alcohol, boiling water, and ether) determination (*2, 4–6*); chemical reactions (*1–6, 8, 12–14*); and thin-layer chromatographic analysis employing barbaloin as the reference standard (*4–7*).

Purity tests

Microbiology

The test for *Salmonella* spp. in aloe products should be negative. The maximum acceptable limits of other microorganisms are as follows (*16–18*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Adulterants: Aloe in commerce may sometimes be adulterated with black catechu, pieces of iron, and stones. These can be detected by examining alcohol-soluble extracts under ultraviolet light which gives a deep brown colour with aloe and a black colour with catechu (*14*).

Total ash

Not more than 2% (*3–5*).

Water-soluble extracts

Not less than 50% (*1*, *2*, *14*).

Alcohol-insoluble extracts

Not more than 10% (*1*–*3*, *14*).

Moisture

Not more than 10% for Cape Aloe (*6*), and not more than 12% for Curacao or Barbados Aloe (*2*–*6*, *14*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Aloe is not more than 0.05 mg/kg (*18*). For other pesticides, see the WHO guidelines on quality control methods for medicinal plants (*16*) and guidelines for predicting dietary intake of pesticide residues (*19*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*16*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*16*).

Other tests

Acid-insoluble ash and chemical tests to be established in accordance with national requirements.

Chemical assays

Thin-layer chromatography and microchemical analyses are employed for the qualitative analysis for the presence of anthracene glycosides (*1*–*7*, *12*, *14*). Quantitative analysis of total anthracene glycosides, calculated as barbaloin, is performed by spectrophotometry (*4*, *5*).

Curacao or Barbados Aloe, derived from Aloe vera (L.) Burm. f.

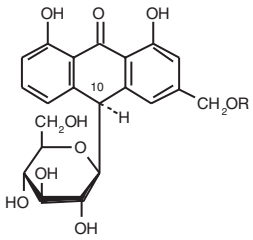
Contains not less than 28% of hydroxyanthracene derivatives, expressed as barbaloin (*4*–*6*).

Cape Aloe, derived from A. ferox Miller and its hybrids with A. africana Mill. and A. spicata Baker

Contains not less than 18% of hydroxyanthracene derivatives, expressed as barbaloin (*4*, *5*).

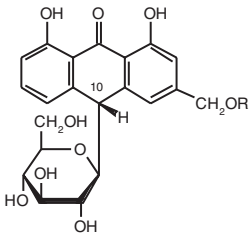
Major chemical constituents

Aloe contains as its major and active principles hydroxyanthrone derivatives, mainly of the aloe-emodin-anthrone 10-*C*-glucoside type. The major constituent is known as barbaloin (aloin) (15–40%) (*8*, *13*). It also contains hydroxyaloin (about 3%). Barbaloin (=aloin) is in fact a mixture of aloin A (10*S*) [**1**] and B (10*R*) [**2**]. *A. ferox* also contains aloinoside A [**3**] and B [**4**]. Aloin A and B interconvert through the anthranol form as do aloinoside A and B (*13*).



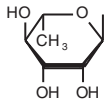
[1] R = H

[3] R = α-L-rhamnopyranosyl



[2] R = H

[4] R = α-L-rhamnopyranosyl



α-L-rhamnopyranosyl
or
6-deoxy-α-L-mannopyranosyl

Dosage forms

Powdered, dried juice and preparations thereof for oral use.

Medicinal uses

Uses supported by clinical data

Short-term treatment of occasional constipation (*2*, *12*, *13*, *15*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of seborrhoeic dermatitis, peptic ulcers, tuberculosis, and fungal infections, and for reduction of blood sugar (glucose) levels (*11*, *20*).

Pharmacology

Experimental pharmacology

As shown for senna, Aloe's mechanism of action is twofold. It stimulates colonic motility, augmenting propulsion and accelerating colonic transit, which reduces fluid absorption from the faecal mass. It also increases paracellular permeability across the colonic mucosa probably owing to an inhibition of Na^+, K^+-adenosine triphosphatase or to an inhibition of chloride channels (*8*, *21*, *22*), which results in an increase in the water content in the large intestine (*21*).

Clinical pharmacology

The laxative effects of Aloe are due primarily to the 1, 8-dihydroxyanthracene glycosides, aloin A and B (formerly designated barbaloin) (*23*, *24*). After oral administration aloin A and B, which are not absorbed in the upper intestine, are hydrolysed in the colon by intestinal bacteria and then reduced to the active metabolites (the main active metabolite is aloe-emodin-9-anthrone) (*25*, *26*), which like senna acts as a stimulant and irritant to the gastrointestinal tract (*27*). The laxative effect of Aloe is not generally observed before 6 hours after oral administration, and sometimes not until 24 or more hours after.

Toxicity

The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored in all recipients, especially in children and the elderly (*28*).

Contraindications

As with other stimulant laxatives, products containing Aloe should not be used in patients with intestinal obstruction or stenosis, atony, severe dehydration with electrolyte depletion, or chronic constipation (*28*). Aloe should not be administered to patients with inflammatory intestinal diseases, such as appendicitis, Crohn disease, ulcerative colitis, irritable bowel syndrome, or diverticulitis, or to children under 10 years of age. Aloe should not be used during pregnancy or lactation except under medical supervision after evaluating benefits and risks. Aloe is also contraindicated in patients with cramps, colic, haemorrhoids, nephritis, or any undiagnosed abdominal symptoms such as pain, nausea, or vomiting (*28*, *29*).

Warnings

Aloe-containing products should be used only if no effect can be obtained through a change of diet or use of bulk-forming products. Stimulant laxative products should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement within 24 hours

after use of a laxative may indicate a serious condition. Chronic use may cause dependence and need for increased dosages, disturbances of water and electrolyte balance (e.g. hypokalaemia), and an atonic colon with impaired function (*28*).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.

Chronic abuse with diarrhoea and consequent fluid and electrolyte losses (mainly hypokalaemia) may cause albuminuria and haematuria, and may result in cardiac and neuromuscular dysfunction, the latter particularly in the case of concomitant use of cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root (see Precautions below).

Precautions

General

Laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, owing to the danger of electrolyte imbalance.

Drug interactions

Decreased intestinal transit time may reduce absorption of orally administered drugs (*30*).

Existing hypokalaemia resulting from long-term laxative abuse can potentiate the effects of cardiotonic glycosides (digitalis, strophanthus) and antiarrhythmic drugs such as quinidine (*30*). The induction of hypokalaemia by drugs such as thiazide diuretics, adrenocorticosteroids, and liquorice root may be enhanced, and electrolyte imbalance may be aggravated (*31*).

Drug and laboratory test interactions

Standard methods may not detect anthranoid metabolites, so measurements of faecal excretion may not be reliable (*26*).

Urinary excretion of certain anthranoid metabolites may discolour the urine, which is not clinically relevant but which may cause false positive results for urinary urobilinogen, and for estrogens when measured by the Kober procedure (*30*).

Carcinogenesis, mutagenesis, impairment of fertility

Data on the carcinogenicity of Aloe are not available. While chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (*32–35*).

In vitro (gene mutation and chromosome aberration tests) and *in vivo* (micronucleus test in murine bone marrow) genotoxicity studies, as well as human and animal pharmacokinetic data, indicate no genotoxic risk from Cape Aloe (*36–38*).

Pregnancy: teratogenic effects

No teratogenic or fetotoxic effects were seen in rats after oral treatment with aloe extract (up to 1000 mg/kg) or aloin A (up to 200 mg/kg) (*39*).

Pregnancy: non-teratogenic effects

Aloe should not be used during pregnancy except under medical supervision after benefits and risks have been evaluated (*40*).

Nursing mothers

Anthranoid metabolites appear in breast milk. *Aloe* should not be used during lactation except under medical supervision, as there are insufficient data available to assess the potential for pharmacological effects in the breast-fed infant (*30*, *40*).

Paediatric use

Oral use of Aloe in children under 10 years old is contraindicated.

Adverse reactions

Abdominal spasms and pain may occur after even a single dose. Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools (*28*).

Chronic abuse of anthraquinone stimulant laxatives can lead to hepatitis (*41*). Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis, malabsorption, weight loss, albuminuria, and haematuria (*30*, *42*, *43*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used (*31*). Secondary aldosteronism may occur owing to renal tubular damage after aggravated use. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been observed, as have excessive excretion of calcium in the stools and osteomalacia of the vertebral column (*44*, *45*). Melanotic pigmentation of the colonic mucosa (pseudomelanosis coli) has been observed in individuals taking anthraquinone laxatives for extended time periods (*29*, *42*). The pigmentation is clinically harmless and usually reversible within 4 to 12 months after the drug is discontinued (*29*, *42*). Conflicting data exist on other toxic effects such as intestinal-neuronal damage after long-term use (*42*, *46*).

Posology

The correct individual dose is the smallest amount required to produce a soft-formed stool (*26*). As a laxative for adults and children over 10 years old, 0.04–0.11 g (Curacao or Barbados Aloe) or 0.06–0.17 g (Cape Aloe) of the dried juice (*6*, *14*), corresponding to 10–30 mg hydroxyanthraquinones per day, or 0.1 g as a single dose in the evening.

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Aloe Vera Gel

Definition

Aloe Vera Gel is the colourless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of *Aloe vera* (L) Burm. f. (Liliaceae) (*1*, *2*).

Synonyms

Aloe barbadensis Mill., *Aloe chinensis* Bak., *A. elongata* Murray, *A. indica* Royle, *A. officinalis* Forsk., *A. perfoliata* L., *A. rubescens* DC, *A. vera* L. var. *littoralis* König ex Bak., *A. vera* L. var. *chinensis* Berger, *A. vulgaris* Lam. (*2–5*). Most formularies and reference books regard *Aloe barbadensis* Mill. as the correct species name, and *Aloe vera* (L.) Burm. f. as a synonym. However, according to the International Rules of Botanical Nomenclature, *Aloe vera* (L.) Burm. f. is the legitimate name for this species (*2–4*). The genus *Aloe* has also been placed taxonomically in a family called Aloeaceae.

Selected vernacular names

Aloe vera gel, aloe gel.

Description

Succulent, almost sessile perennial herb; leaves 30–50 cm long and 10 cm broad at the base; colour pea-green (when young spotted with white); bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike; stamens frequently project beyond the perianth tube (*6*).

Plant material of interest: liquid gel from the fresh leaf

Aloe Vera Gel is not to be confused with the juice, which is the bitter yellow exudate originating from the bundle sheath cells of the leaf. The drug Aloe consists of the dried juice, as defined on page 33.

General appearance

The gel is a viscous, colourless, transparent liquid.

Organoleptic properties

Viscous, colourless, odourless, taste slightly bitter.

Microscopic characteristics

Not applicable.

Geographical distribution

Probably native to north Africa along the upper Nile in the Sudan, and subsequently introduced and naturalized in the Mediterranean region, most of the tropics and warmer areas of the world, including Asia, the Bahamas, Central America, Mexico, the southern United States of America, south-east Asia, and the West Indies (*2*).

General identity tests

To be established in accordance with national requirements.

Purity tests

Microbiology

The test for *Salmonella* spp. in Aloe Vera Gel should be negative. Acceptable maximum limits of other microorganisms are as follows (*7–9*). For external use: aerobic bacteria—not more than 10^2/ml; fungi—not more than 10^2/ml; enterobacteria and certain Gram-negative bacteria—not more than 10^1/ml; *Staphylococcus* spp.—0/ml. (Not used internally.)

Moisture

Contains 98.5% water (*10*).

Pesticide residues

To be established in accordance with national requirements. For guidance, see WHO guidelines on quality control methods for medicinal plants (*7*) and guidelines on predicting dietary intake of pesticide residues (*11*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form (*7*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*7*).

Other tests

Chemical tests for Aloe Vera Gel and tests for total ash, acid-insoluble ash, alcohol-soluble residue, foreign organic matter, and water-soluble extracts to be established in accordance with national requirements.

Chemical assays

Carbohydrates (0.3%) (*12*), water (98.5%) (*10*). Polysaccharide composition analysis by gas–liquid chromatography (*13*).

Major chemical constituents

Aloe Vera Gel consists primarily of water and polysaccharides (pectins, hemicelluloses, glucomannan, acemannan, and mannose derivatives). It also contains amino acids, lipids, sterols (lupeol, campesterol, and β-sitosterol), tannins, and enzymes (*1*). Mannose 6-phosphate is a major sugar component (*14*).

Dosage forms

The clear mucilaginous gel. At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended. Preparation of fresh gel: harvest leaves and wash them with water and a mild chlorine solution. Remove the outer layers of the leaf including the pericyclic cells, leaving a "fillet" of gel. Care should be taken not to tear the green rind which can contaminate the fillet with leaf exudate. The gel may be stabilized by pasteurization at 75–80 °C for less than 3 minutes. Higher temperatures held for longer times may alter the chemical composition of the gel (*2*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Aloe Vera Gel is widely used for the external treatment of minor wounds and inflammatory skin disorders (*1*, *14*–*17*). The gel is used in the treatment of minor skin irritations, including burns, bruises, and abrasions (*1*, *14*, *18*). The gel is further used in the cosmetics industry as a hydrating ingredient in liquids, creams, sun lotions, shaving creams, lip balms, healing ointments, and face packs (*1*).

Aloe Vera Gel has been traditionally used as a natural remedy for burns (*18*, *19*). Aloe Vera Gel has been effectively used in the treatment of first- and second-degree thermal burns and radiation burns. Both thermal and radiation burns healed faster with less necrosis when treated with preparations containing Aloe Vera Gel (*18*, *19*). In most cases the gel must be freshly prepared because of its sensitivity to enzymatic, oxidative, or microbial degradation. Aloe Vera Gel is not approved as an internal medication, and internal administration of the gel has not been shown to exert any consistent therapeutic effect.

Uses described in folk medicine, not supported by experimental or clinical data

The treatment of acne, haemorrhoids, psoriasis, anaemia, glaucoma, petit ulcer, tuberculosis, blindness, seborrhoeic dermatitis, and fungal infections (*2*, *6*, *19*).

Pharmacology

Wound healing

Clinical investigations suggest that Aloe Vera Gel preparations accelerate wound healing (*14*, *18*). *In vivo* studies have demonstrated that Aloe Vera Gel promotes wound healing by directly stimulating the activity of macrophages and fibroblasts (*14*). Fibroblast activation by Aloe Vera Gel has been reported to increase both collagen and proteoglycan synthesis, thereby promoting tissue repair (*14*). Some of the active principles appear to be polysaccharides composed of several monosaccharides, predominantly mannose. It has been suggested that mannose 6-phosphate, the principal sugar component of Aloe Vera Gel, may be partly responsible for the wound healing properties of the gel (*14*). Mannose 6-phosphate can bind to the growth factor receptors on the surface of the fibroblasts and thereby enhance their activity (*14*, *15*).

Furthermore, acemannan, a complex carbohydrate isolated from *Aloe* leaves, has been shown to accelerate wound healing and reduce radiation-induced skin reactions (*20*, *21*). The mechanism of action of acemannan appears to be twofold. First, acemannan is a potent macrophage-activating agent and therefore may stimulate the release of fibrogenic cytokines (*21*, *22*). Second, growth factors may directly bind to acemannan, promoting their stability and prolonging their stimulation of granulation tissue (*20*).

The therapeutic effects of Aloe Vera Gel also include prevention of progressive dermal ischaemia caused by burns, frostbite, electrical injury and intra-arterial drug abuse. *In vivo* analysis of these injuries demonstrates that Aloe Vera Gel acts as an inhibitor of thromboxane A_2, a mediator of progressive tissue damage (*14*, *17*). Several other mechanisms have been proposed to explain the activity of Aloe Vera Gel, including stimulation of the complement linked to polysaccharides, as well as the hydrating, insulating, and protective properties of the gel (*1*).

Because many of the active ingredients appear to deteriorate on storage, the use of fresh gel is recommended. Studies of the growth of normal human cells *in vitro* demonstrated that cell growth and attachment were promoted by exposure to fresh *Aloe vera* leaves, whereas a stabilized Aloe Vera Gel preparation was shown to be cytotoxic to both normal and tumour cells. The cytotoxic effects of the stabilized gel were thought to be due to the addition of other substances to the gel during processing (*23*).

Anti-inflammatory

The anti-inflammatory activity of Aloe Vera Gel has been revealed by a number of *in vitro* and *in vivo* studies (*14*, *17*, *24*, *25*). Fresh Aloe Vera Gel significantly

reduced acute inflammation in rats (carrageenin-induced paw oedema), although no effect on chronic inflammation was observed (*25*). Aloe Vera Gel appears to exert its anti-inflammatory activity through bradykinase activity (*24*) and thromboxane B_2 and prostaglandin F_2 inhibition (*18*, *26*). Furthermore, three plant sterols in Aloe Vera Gel reduced inflammation by up to 37% in croton oil-induced oedema in mice (*15*). Lupeol, one of the sterol compounds found in *Aloe vera*, was the most active and reduced inflammation in a dose-dependent manner (*15*). These data suggest that specific plant sterols may also contribute to the anti-inflammatory activity of Aloe Vera Gel.

Burn treatment

Aloe Vera Gel has been used for the treatment of radiation burns (*27–30*). Healing of radiation ulcers was observed in two patients treated with *Aloe vera* cream (*27*), although the fresh gel was more effective than the cream (*29*, *30*). Complete healing was observed, after treatment with fresh Aloe Vera Gel, in two patients with radiation burns (*30*). Twenty-seven patients with partial-thickness burns were treated with Aloe Vera Gel in a placebo-controlled study (*31*). The Aloe Vera Gel-treated lesions healed faster (11.8 days) than the burns treated with petroleum jelly gauze (18.2 days), a difference that is statistically significant (*t*-test, $P < 0.002$).

Contraindications

Aloe Vera Gel is contraindicated in cases of known allergy to plants in the Liliaceae.

Warnings

No information available.

Precautions

No information available concerning general precautions, or precautions dealing with carcinogenesis, mutagenesis, impairment of fertility; drug and laboratory test interactions; drug interactions; nursing mothers; paediatric use; or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

There have been a few reports of contact dermatitis and burning skin sensations following topical applications of Aloe Vera Gel to dermabraded skin (*18*, *32*). These reactions appeared to be associated with anthraquinone contaminants in this preparation (*33*). A case of disseminated dermatitis has been reported following application of Aloe Vera Gel to a patient with stasis dermatitis (*34*). An acute bullous allergic reaction and contact urticaria have also been reported to result from the use of Aloe Vera Gel (*35*).

Posology

Fresh gel or preparations containing 10–70% fresh gel.

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Radix Astragali

Definition

Radix Astragali is the dried root of *Astragalus membranaceus* (Fisch.) Bunge and *Astragalus mongholicus* Bunge (Fabaceae) (*1*, *2*).

Synonyms

Fabaceae are also known as Leguminosae.

Astragalus membranaceus (Fisch.) Bunge

A. propinguus B. Schischk. (*3*).

Astragalus mongholicus Bunge

A. membranaceus (Fisch.) Bunge var. *mongholicus* (Bunge) Hsiao (*3*).

Selected vernacular names

Astragalus root, hoàng kỳ, huang-chi, huangoi, huangqi, huángqi, hwanggi, membranous milkvetch, milkvetch, Mongolian milk-vetch, neimeng huangqi, ogi, ougi, zhongfengnaomaitong (*1*, *3*–*9*).

Description

Astragalus membranaceus (Fisch.) Bunge

Perennial herb, 25–40 cm tall. Leaves 3–6 cm long; petiole obsolete; stipules free, cauline, green, triangular ovate, sparingly vested on the outside with white hair. Leaflets oblong-obovate, oval or oblong-oval. Racemes oblong-ovoid to ovoid, 4–5 cm long, 10–15 flowers; bracts lanceolate. Calyx 8–9 mm long, campanulate, strongly oblique, glabrous. Corolla yellowish, 18–20 mm long. Ovary glabrous (*4*). Root cylindrical or nearly cylindrical with small bases of lateral root dispersed on the surface, and usually not branched; greyish yellow to yellowish brown epidermis and fibrous fracture (*2*, *5*).

Astragalus mongholicus Bunge

Perennial herb, 60–150 cm tall. Leaves pinnate, leaflets broadly elliptical. Raceme axillary. Calyx tubular 5 mm long. Corolla yellowish; pod ovate-

Fructus Bruceae

Definition

Fructus Bruceae consists of the dried ripe fruits of *Brucea javanica* (L.) Merr. (Simaroubaceae) (*1*, *2*).

Synonyms

Brucea amarissima Desv. ex Gomes, *B. sumatrana* Roxb., *Gonus amarissimus* Lour., *Lussa amarissima* O. Ktze (*2*, *3*).

Selected vernacular names

Biji makassar, bulah makassar, Java brucea, k'u-shen-tzu, kho sam, ko-sam, ku-sheng-tzu, nha dàm tùr, raat cha dat, raat dat, ratchadat, sàu dau rùng, xoan rùng, ya tan tzu, ya-dan-zi, yadãnzi (*1*–*7*).

Description

A shrub or small tree, 1–3 m high; younger parts softly pubescent. Leaves compound-paripinnate; leaflets 5–11, oval-lanceolate, 5–10 cm long by 2–4 cm wide; apex acuminate, base broadly cuneate and often somewhat oblique; margin serrate; both surfaces densely pubescent, especially the underside. Flowers minute, purple, in numerous small cymes or clusters collected into axillary panicles. Sepals 4, connate at the base. Petals 4, villous, glandular at the tips. Male flowers, stamens 4, pistil reduced to a stigma; female flowers, stamens 4, much reduced. Ovary with 4 free carpels. Fruit and drupe ovoid, black when ripe. Seeds, compressed, rugose, blackish brown (*3*–*5*).

Plant material of interest: dried ripe fruit or seed

Fruit also refers to the kernel or seed with the pulp removed (*3*, *4*).

General appearance

The fruit is ovoid, 6–10 mm long by 4–7 mm in diameter. Externally black or brown, with raised reticulate wrinkles, the lumen irregularly polygonal, obviously ribbed at both sides. Apex acuminate, base having a dented fruit stalk scar, shell hard and brittle. Seeds ovoid, 5–6 mm long by 3–5 mm in diameter, externally yellowish white, reticulate; testa thin, cotyledons milky white and oily (*1*, *3*, *4*).

Organoleptic properties

Odour slight; taste, very bitter (*1*, *4*).

Microscopic characteristics

The pulverized pericarp is brown. Epidermal cells polygonal, with brown cellular contents; parenchymatous cells polygonal, containing clusters of calcium oxalate prisms, up to 30 mm in diameter. Stone cells subrounded or polygonal, 14–38 mm in diameter (*1*).

Powdered plant material

Powdered seeds yellowish white. Testa cells polygonal and slightly elongated. Endosperm and cotyledon cells contain aleurone grains (*1*).

Geographical distribution

Indigenous to China, India, Indonesia, and Viet Nam (*3*, *4*).

General identity tests

Macroscopic and microscopic examinations (*1*, *3*, *4*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Fructus Bruceae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*8–10*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations (capsules) for internal use: aerobic bacteria—not more than 10^5/g; fungi—not more than 10^4/g; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g; *Escherichia coli*—0/g.

Foreign organic matter

Not more than 2% (*2*).

Total ash

Not more than 6% (*2*).

Acid-insoluble ash

Not more than 0.6% (*2*).

Radix Bupleuri

Definition

Radix Bupleuri consists of the dried root of *Bupleurum falcatum* L. or *B. falcatum* L. var. *scorzonerifolium* (Willd.) Ledeb. (Apiaceae) (*1*, *2*).

Synonyms

Bupleurum chinense D.C. and *B. scorzonerifolium* Willd. have been treated as different species (*1*) but are actually synonyms of *B. falcatum* L. var. *scorzonerifolium* (*3*). Apiaceae are also referred to as Umbelliferae.

Selected vernacular names

Beichaihu, bupleurum root, ch'ai hu, chaifu, chaihu, chaiku-saiko, Chinese thorowax root, juk-siho, kara-saiko, mishima-saiko, nanchaihu, northern Chinese thorowax root, radix bupleur, saiko, shi ho, shoku-saiko, wa-saiko, Yama-saiko (*1–5*).

Description

A perennial herb up to 1 m tall; base woody and the rhizome branching. Stem slender, flexuous, branches spreading. Basal leaves lanceolate, upper lamina broad, lower narrowed into a petiole, veins 7, apex acute, mucronate; middle and upper leaves linear to lanceolate, gradually shorter, falcate, veins 7–9, base slightly amplexicaul, apex acuminate. Involucre of 1–3 minute bracts or lacking. Rays 5–8. Involucel of 5 minute, 3-veined bractlets, shorter than the flowering umbellet. Pedicels shorter than the fruits. Fruit oblong, 3–4 mm long; furrows 3-vittate (*4*, *6*).

Plant material of interest: dried roots

General appearance

Single or branched root, of long cone or column shape, 10–20 cm in length, 0.5–1.5 cm in diameter; occasionally with remains of stem on crown; externally light brown to brown and sometimes with deep wrinkles; easily broken, and fractured surface somewhat fibrous (*2*).

Organoleptic properties

Odour, characteristic, slightly aromatic to rancid; taste, slightly bitter (*1*, *2*).

Microscopic characteristics

Transverse section reveals often tangentially extended clefts in cortex, the thickness reaching a third to a half of the radius, and cortex scattered with a good many intercellular schizogenous oil canals 1.5–3.5 cm in diameter; vessels lined radially or stepwise in xylem, with scattered fibre groups; in the crown pith also contains oil canals; parenchyma cells filled with starch grains and some oil drops. Starch grains composed of simple grains, 2–10 μm in diameter, or compound grains (*2*).

Powdered plant material

Information not available. Description to be established by appropriate national authorities.

Geographical distribution

Indigenous to northern Asia, northern China, and Europe (*4*, *6*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*), microchemical detection for saponins (*1*, *2*), and thin-layer chromatographic analysis for triterpene saponins with reference to saikosaponins (*2*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Bupleuri should be negative. The maximum acceptable limits of other microorganisms are as follows (*7–9*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g.

Chemical

Contains triterpene saponins (saikosaponins). Quantitative level to be established by appropriate national authorities, but should be not less than 1.5% according to literature data.

Foreign organic matter

Not more than 10% of stems and leaves (*2*). No roots of *B. longiradiantum* Turcz., which is toxic (*1*, *5*). Not more than 1% of other foreign matter (*2*).

Total ash

Not more than 6.5% (*2*).

Acid-insoluble ash

Not more than 2% (*2*).

Dilute ethanol-soluble extractive

Not less than 11% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Bupleuri is not more than 0.05 mg/kg (*9*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*7*) and WHO guidelines for predicting dietary intake of pesticide residues (*10*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*7*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*7*).

Other tests

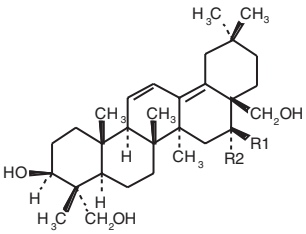
Tests for moisture and for water-soluble extractive to be established by national authorities.

Chemical assays

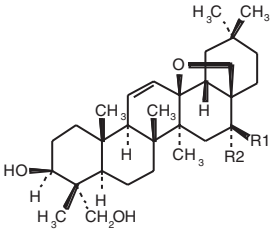
Total saikosaponins determination by colorimetric analysis (*11*), and high-performance liquid chromatography analysis for saikosaponins A, B_1, B_2, and D (*12*, *13*).

Major chemical constituents

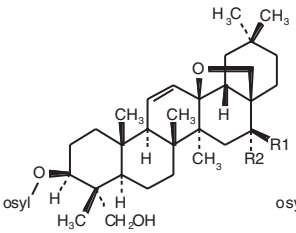
The major constituents are triterpene saponins, including saikosaponins A, $B_{1–4}$, D, E, F and H and related compounds including saikogenins A–G (*5*, *14*). Two biologically active polysaccharides, bupleurans 2IIb and 2IIc, have also been isolated from the roots of *B. falcatum* (*15*, *16*). Representative structures of saikosaponins are presented in the figure.



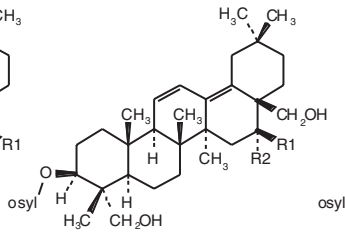
saikogenin A R1 = OH , R2 = H
saikogenin D R1 = H , R2 = OH



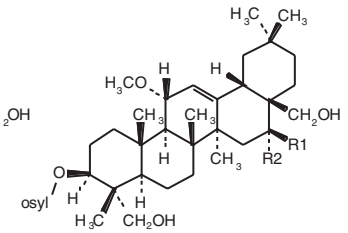
saikogenin F R1 = OH , R2 = H
saikogenin G R1 = H , R2 = OH



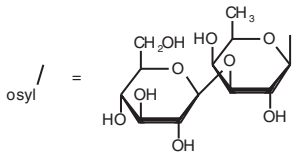
saikosaponin A R1 = OH , R2 = H
saikosaponin D R1 = H , R2 = OH



saikosaponin B_1 R1 = OH , R2 = H
saikosaponin B_2 R1 = H , R2 = OH



saikosaponin B_3 R1 = OH , R2 = H
saikosaponin B_4 R1 = H , R2 = OH



3-*O*-β-D-glucopyranosyl-β-D-fucopyranosyl

or

3-*O*-β-D-glucopyranosyl-6-deoxy-β-D-galactopyranosyl

Dosage forms

Decoction (*5*). Store crude plant material in a dry environment protected from moths, light, and moisture (*1, 2*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of fever, pain, and inflammation associated with influenza, and the common cold (*1, 2, 5*). The drug is also used as an analgesic for the treatment of distending pain in the chest and hypochondriac regions, and for amenorrhoea (*1*). Extracts have been used for the treatment of chronic hepatitis, nephrotic syndrome, and autoimmune diseases (*1, 5*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of deafness, dizziness, diabetes, wounds, and vomiting (*5*).

Pharmacology

Experimental pharmacology

Antipyretic and analgesic activity

A number of *in vivo* studies have confirmed the antipyretic activity of Radix Bupleuri in the treatment of induced fevers in animals. Oral administration of a *Bupleurum* decoction (5 g/kg) to rabbits with a heat-induced fever decreased body temperature to normal levels within 1.5 hours (*5*). Subcutaneous injection of an aqueous ethanol extract of *Bupleurum* roots (2.2 ml/kg, 1.1 g crude drug/ml) significantly reduced fevers in rabbits injected with *Escherichia coli* (*17*).

Oral administration of saikosaponins to rats produced hypothermic and antipyretic effects (*5*). Furthermore, intraperitoneal injection of the volatile oil (300 mg/kg) or saponins (380 and 635 mg/kg) isolated from *B. chinense* (*B. falcatum)* roots effectively decreased fever in mice induced by yeast injections (*18*). Oral administration of 200–800 mg/kg of a crude saponin fraction to mice produced sedative, analgesic, and antipyretic effects, but no anticonvulsant effect or reduction in muscle tone was observed (*14*). Saikosaponins are believed to be the major active antipyretic constituents in Radix Bupleuri extracts.

Analgesic activity of *Bupleurum* extracts is also supported by *in vivo* studies. Injections of a crude *Bupleurum* extract or purified sapogenin A inhibited writhing induced by intraperitoneal injection of acetic acid in mice (*5*). The saikosaponins appear to be the active analgesic constituents of the drug. Intraperitoneal injection of mice with a total saponin fraction derived from *B. chinense* (*B. falcatum*) produced a marked analgesic effect on the pain induced by electroshock (5). Moreover, orally administered saikosaponins were reported to have an analgesic effect in mice (tail pressure test) (*5*).

Sedative effects

In vivo studies have also confirmed the sedative effects of Radix Bupleuri. Both the crude saikosaponin fraction and saikogenin A are reported to have significant sedative effects (*5*). *In vivo* studies, using the rod climbing test, demonstrated that the sedative effect of the saikosaponins (200–800 mg/kg) in mice was similar to that of meprobamate (100 mg) (*5*). Oral administration of saikosides extracted from *B. chinense* (*B. falcatum*) or saikosaponin A has also been reported to prolong cyclobarbital sodium-induced sleep (*5*). Furthermore, intraperitoneal injection of saikogenin A inhibited rod climbing in mice and antagonized the stimulant effects of metamfetamine and caffeine (*5*).

Anti-inflammatory activity

Anti-inflammatory activity of Radix Bupleuri has been demonstrated by *in vivo* studies. Intraperitoneal injection of the saponin fraction, the volatile oil, or a crude extract from *B. chinense* (*B. falcatum*) significantly inhibited carrageenin-induced rat paw oedema (*5*). The saikosaponins are the active anti-inflammatory constituents of the drug (*19*, *20*). Oral administration of a crude saikosaponin fraction (2 g/kg) from *B. falcatum* inhibited dextran-, serotonin-, or croton oil-induced rat paw oedema (*5*, *21*). Structure–activity correlations have revealed that saikosaponins A and D both have anti-inflammatory activity, while saikosaponin C does not (*22*). The potency of anti-inflammatory activity of the saikosaponins is similar to that of prednisolone (*5*).

Immune regulation activity

In vitro studies have demonstrated that a hot-water extract from the root of *B. falcatum* enhanced the antibody response and inhibited mitogen-induced lymphocyte transformation (*23*). An acidic pectic polysaccharide, bupleuran 2IIb, isolated from the roots of *B. falcatum,* was found to be a potent enhancer of immune complex binding to macrophages (*24*). The activity of this polysaccharide appeared to be due to its ability to enhance the Fc receptor function of macrophages. This study has shown that the binding of glucose oxidase–antiglucose oxidase complexes (a model of immune complexes) to murine peritoneal macrophages was stimulated by treatment with the polysaccharide (*24*). Bupleuran 2IIb appears to up-regulate both FcRI and FcRII receptor expression on the macrophage surface in a dose-dependent manner (*25*). The up-regulation of the Fc receptor by bupleuran 2IIb depends on an increase in intracellular calcium and activation of calmodulin (*25*). Only saikosaponin D has been shown to enhance Fc receptor expression of thioglycollate-elicited murine peritoneal macrophages *in vitro* (*26*). This activity appears to be due to the translocation of FcR from the internal pool to the cell surface. *In vitro* studies with saikosaponin D have shown that this compound was able to control bidirectionally the growth response of T lymphocytes stimulated by concanavalin A, anti-CD3 monoclonal antibody, and calcium ionophore A23187 plus phorbol 12-myristate 13-acetate (*27*). Saikosaponin D also promoted interleukin-2 production and receptor expression, as well as c-fos gene transcription (*28*). The results of this study suggest that saikosaponin D exerts its immunostimulant effects by modification of T lymphocyte function (*28*).

Antiulcer activity

Antiulcer activity of Radix Bupleuri has been demonstrated both *in vivo* and *in vitro*. A polysaccharide fraction of a hot-water extract of the root of *B. falcatum* was reported to inhibit significantly hydrochloric acid- or ethanol-induced ulcerogenesis in mice (*15*). The polysaccharide fraction (BR-2, 100 mg/kg) had potent antiulcer activity, and its activity was similar to that of sucralfate (100 mg/kg) (*29*). BR-2 significantly protected against a variety of gastric lesions,

water-immersion stress ulcer and pylorus-ligation ulcer in mice and rats (*29*). By oral, intraperitoneal, or subcutaneous administration, BR-2 was further found to be effective against hydrochloric acid- or ethanol-induced gastric lesions suggesting that BR-2 acted both locally and systemically (*29*). The mechanism of antiulcer action appears to be due to a reinforcement of the protective mucosal barrier as well as an antisecretory action on acid and pepsin (*30*). Saponins isolated from *B. falcatum* root have also been reported to have weak antiulcer activity in the pylorus-ligation ulcer model (*30*).

Hepatoprotectant activity

Crude saponins of *B. falcatum*, administered orally to rats at a daily dose of 500 mg/kg for 3 days, normalized liver functions as determined by serum alkaline phosphatase levels in rats treated with carbon tetrachloride (*31*). Treatment of rats with saikosaponins 2 hours before treatment with D-galactosamine inhibited the increase in serum aspartate aminotransferase and alanine aminotransferase levels produced by damage of liver tissues (*31*). Conversely, saikosaponins did not affect an increase in serum alanine aminotransferase and experimental cirrhosis in rats caused by carbon tetrachloride intoxication (*32*).

Clinical pharmacology

Antipyretic activity

The antipyretic activity of *B. chinense* (*B. falcatum*) has been investigated in patients with fevers caused by the common cold, influenza, malaria, and pneumonia (*5*). In one clinical study of 143 patients treated with the herb, fevers subsided within 24 hours in 98.1% of all cases of influenza, and in 87.9% of all cases of the common cold (*5*, *33*). In another study, 40 patients with fever of pathological origin had a significant reduction in fever (1–2 °C), but the antipyretic effect of Radix Bupleuri in these patients was transient unless combined with antibiotic therapy (*5*, *34*).

Contraindications

No information available.

Warnings

Radix Bupleuri causes sedation when used in large doses (*5*); therefore, patients should be cautious when operating a motor vehicle or hazardous machinery.

Precautions

Drug interactions

The use of alcohol, sedatives and other central nervous system depressants in conjunction with Radix Bupleuri may cause synergistic sedative effects. No clinical studies have evaluated this possible interaction; however, patients

should be cautioned about taking the drug with alcohol, sedatives, or other drugs known to cause depression of the central nervous system.

Carcinogenesis, mutagenesis, impairment of fertility

Methanolic extracts of *B. chinense* (*B. falcatum*) were not mutagenic in the modified Ames test using *Salmonella typhimurium* TA 98 and TA 100, in the presence or absence of rat liver S-9 mix (*35*, *36*). Furthermore, hot-water extracts of *Bupleurum* were shown to have antimutagenic activity in AFB1-induced mutagenesis in the mouse *Salmonella typhi*/mammalian microsomal system (Ames test) (strain TA 98) and in the *in vivo* mouse bone marrow cell chromosome aberration and mouse bone marrow eosinophil micronucleus test (*37*). There is one report that a hot-water extract of *B. falcatum* enhanced the mutagenic activity of Trp-P-1 with S9 mix in *Salmonella typhimurium* (*38*).

Pregnancy: teratogenic and non-teratogenic effects

No data available; therefore, *B. falcatum* should not be administered during pregnancy.

Nursing mothers

Excretion of the drug into breast milk and its effects on the newborn infant have not been established; therefore, *Bupleurum* should not be administered to nursing women.

Paediatric use

Guidelines for the administration of the drug to children are not available.

Other precautions

No information available concerning general precautions or drug and laboratory test interactions.

Adverse reactions

Mild lassitude, sedation, and drowsiness have been reported as frequent side-effects (*5*). Large doses have also been reported to decrease appetite and cause pronounced flatulence and abdominal distension. Three incidents of allergic reactions were reported in patients given intramuscular injections of the drug (*5*).

Posology

Generally, doses of 3–9 g/day (*1*).

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Water-soluble extractive

Not less than 18% (*2*).

Dilute ethanol-soluble extractive

Not less than 26% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Fructus Bruceae is not more than 0.05 mg/kg (*10*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*8*) and guidelines on predicting dietary intake of pesticide residues (*11*).

Heavy metals

Recommended lead and cadmium levels are no more than 10.0 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*8*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*8*).

Other purity tests

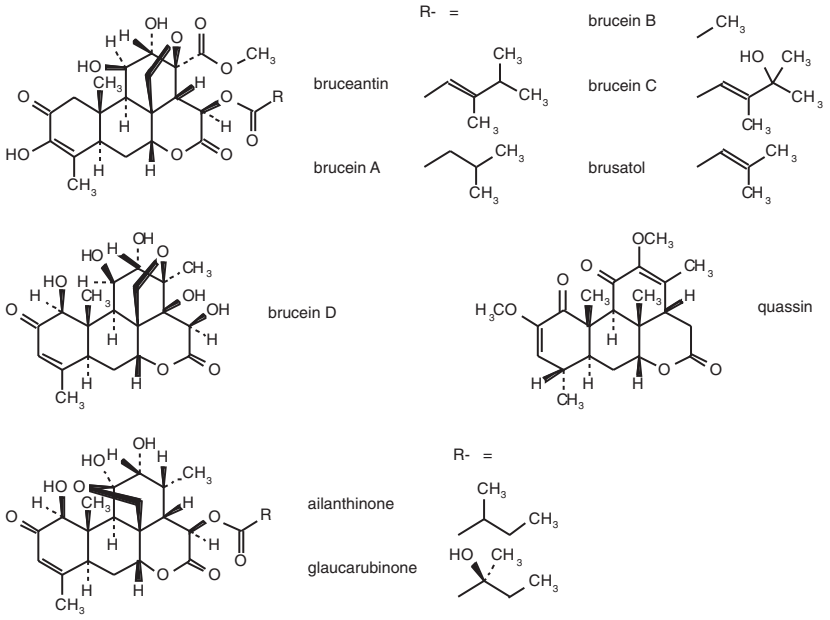
Chemical and moisture tests to be established in accordance with national requirements.

Chemical assays

Contains bruceosides and related quassinoids. Quantitative content requirement to be established. Quantitative determination of quassinoid triterpenes by a high-performance liquid chromatographic method developed for the determination of bruceoside A (*12*).

Major chemical constituents

Quassinoid triterpenes, including bruceantin, bruceantinol, bruceantinoside A, bruceins A–G and Q, brucein E 2-*O*-β-D-glucoside, bruceolide, bruceosides A–C, brusatol, dehydrobruceantinol, dehydrobruceins A and B, dehydrobrusatol, dihydrobrucein A, yadanzigan, yadanziolides A–D, and yadanziosides A–P predominate as the secondary metabolite constituents (*13, 14*). Representative quassinoid structures are presented in the figure.



Dosage forms

Seeds for decoction, or capsules (*1*, *3*, *4*). Store in airtight container, protected from light and moisture (*1*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of amoebic dysentery and malaria (*1*, *3*, *14*, *15*).

Uses described in folk medicine, not supported by experimental or clinical data

As a poultice on boils, to treat ringworm, whipworm, roundworm and tapeworm, scurf, centipede bites, haemorrhoids, and enlarged spleen (*3*–*6*). The seed and seed oil have been used in the treatment of warts and corns (*1*, *4*). Fructus Bruceae has been used in the treatment of trichomoniasis, corns and verrucae (*6*).

Pharmacology

Experimental pharmacology

Amoebicidal and antibacterial activity

A number of *in vitro* studies have indicated that extracts of *Brucea javanica* kernels are effective amoebicides. In one such study, a crude butanol extract of *B. javanica* was highly active against *Entamoeba histolytica* (*16*). This amoebicidal activity was associated with two polar compounds isolated from the extract, bruceantin and brucein C, which are quassinoid constituents (*16*). (*Brucea* quassinoids were active against *E. histolytica* and other protozoa *in vitro* (*17, 18*).) The quassinoids were potent inhibitors of protein synthesis both in mammalian cells and in malaria parasites, and it has been suggested that this effect accounts for their amoebicidal activity (*17*). In one other investigation, brusatol, another quassinoid isolated from the seeds of *B. javanica*, was also reported to be effective in the treatment of dysentery (*19*). Extracts from the kernels of *B. javanica* have also been reported to possess antibacterial activity against *Shigella shiga, S. flexneri, S. boydii, Salmonella lexington, Salmonella derby, Salmonella typhi* type II, *Vibrio cholerae inaba* and *Vibrio cholerae ogawa* (*20*).

Antimalarial activity

Numerous *in vitro* and *in vivo* studies have demonstrated the antiplasmodial activity of Fructus Bruceae extracts. *In vitro* studies have determined that bruceantin, a quassinoid constituent of the drug, exhibited significant antiplasmodial activity against *Plasmodium falciparum* (*21, 22*). Extracts of the drug were also active *in vitro* against chloroquine-resistant *P. falciparum* (*23, 24*) and *in vivo* against *P. berghei* (mice) (*23, 25*). Nine quassinoid constituents of the drug had *in vitro* IC_{50} values of 0.046–0.0008 mg/ml against chloroquine-resistant *P. falciparum* strain K-1 (*23*). Four of these compounds were also active *in vivo* against *P. berghei* infections in mice after oral dosing (*23*), and three of the compounds, bruceins A–C, had *in vitro* activity comparable to that of the antimalarial drug mefloquine (*24*). Bruceolide, another quassinoid constituent of *B. javanica*, was also effective *in vivo* (mice) against *P. berghei*, and was reported to be more effective than chloroquine (*25*). A recent *in vitro* screening of quassinoids against various protozoa showed that brucein D and brusatol have very selective inhibitory activity against *P. falciparum* (*17*).

Quassinoids isolated from *B. javanica* are reported to have cytotoxic activity *in vitro* (*17, 26, 27*). Bruceantin was tested in phase I clinical cancer trials, but no tumour regression was observed (*28, 29*).

Clinical pharmacology

Brucea javanica fruit extracts have been used clinically in the treatment of amoebic dysentery (*14, 15*). These investigations indicated that the antidysenteric activity of the *Brucea* extract was less effective than that of emetine (*14, 15*).

Contraindications

Fructus Bruceae should not be administered to children or pregnant women (*6*).

Warnings

No information available.

Precautions

Pregnancy: teratogenic and non-teratogenic effects

No data available. Preparations containing Fructus Bruceae must not be administered to pregnant women (*6*).

Nursing mothers

Excretion of Fructus Bruceae into breast milk and its effects on infants have not been established; therefore this drug should not be administered to nursing women.

Paediatric use

Fructus Bruceae should not be administered to young children (*6*).

Other precautions

No information available about general precautions or precautions concerning carcinogenesis, mutagenesis, or impairment of fertility; drug interactions; or drug and laboratory test interactions.

Adverse reactions

Some cases of anaphylaxis have been reported after external applications of the fruits of *B. javanica* (*30*).

Posology

Daily dose to treat amoebiasis, 4–16 g as a decoction or powder in three divided doses for 3–7 days (*3*); to treat malaria, 3–6 g in three divided doses after meals for 4 or 5 days (*3*).

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oblong, glabrous, reticulate. The root is flexible and long and covered with a tough, wrinkled, yellowish brown epidermis, which has a tendency to break up into woolly fibres. The woody interior is yellowish white (*6*).

Plant material of interest: root

General appearance

Radix Astragali is cylindrical, some upper branches relatively thick, 30–90 cm long, 1–3.5 cm in diameter. Externally pale brownish yellow or pale brown, with irregular, longitudinal wrinkles or furrows. Texture hard and tenacious, broken with difficulty, fracture highly fibrous and starchy, bark yellowish white, wood pale yellow, with radiate striations and fissures, the centre part of old root occasionally looking like rotten wood, blackish brown or hollowed (*1*).

Organoleptic properties

Colour, pale yellow to yellow-brown; taste, slightly sweet; odour, slight (*1*, *2*, *4*, *7*).

Microscopic characteristics

The transverse section shows cork consisting of many rows of cells. Phelloderm, 3–5 rows of collenchymatous cells. Outer part of phloem rays often curved and fissured, fibres in bundles, walls thickened and lignified or slightly lignified, arranged alternately with sieve tube groups; stone cells sometimes visible near phelloderm. Cambium in a ring. Xylem vessels scattered singly or 2 or 3 aggregated in groups; wood fibres among vessel stone cells singly or 2–4 in groups, sometimes visible in rays. Parenchymatous cells contain starch granules (*1*).

Powdered plant material

Yellowish white. Fibres in bundles or scattered, 8–30 μm in diameter, thick-walled, with longitudinal fissures on the surface, the primary walls often separated from the secondary walls, both ends often tassel-like, or slightly truncated. Bordered-pitted vessels colourless or orange, bordered pits arranged closely. Stone cells occasionally visible, rounded, oblong or irregular, slightly thick-walled (*1*).

Geographical distribution

Indigenous to China, the Democratic People's Republic of Korea, Mongolia, and Siberia (*5*, *6*). Commercially cultivated in northern China and the Democratic People's Republic of Korea (*5*).

General identity tests

Macroscopic and microscopic examination and thin-layer chromatographic analysis for the presence of triterpene saponins (astragaloside I as reference standard) (*1*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Astragali products should be negative. The maximum acceptable limits of other microorganisms are as follows (*10*, *11*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 5.0% (*1*, *2*).

Acid-insoluble ash

Not more than 1.0% (*1*, *2*).

Water-soluble extractive

Not less than 17.0% (*1*).

Moisture

Not more than 13.0% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Radix Astragali is not more than 0.05 mg/kg (*11*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*10*) and WHO guidelines on predicting dietary intake of pesticide residues (*12*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*10*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*10*).

Other tests

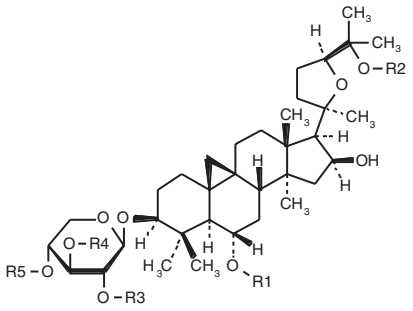
Chemical tests and tests for alcohol-soluble extractive and foreign organic matter are to be established in accordance with national requirements.

Chemical assays

Determination of triterpene saponins (astragalosides I–X) by thin-layer chromatographic analysis (*1*). Concentration limits and quantitative methods need to be established for the triterpene saponins (e.g. astragalosides), as well as for the polysaccharides.

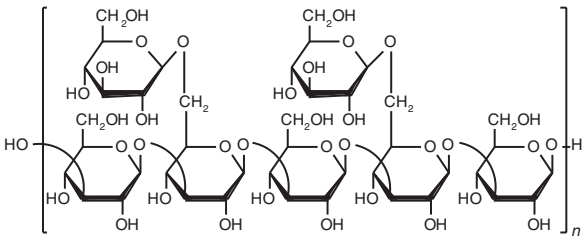
Major chemical constituents

Major chemical constituents are triterpene saponins (astragalosides I–X and isoastragalosides I–IV), and polysaccharides (e.g. astragalan, astraglucan AMem-P) (*3*, *13*).



	R1	R2	R3	R4	R5
astragaloside I	glc *	H	CH_3CO	CH_3CO	H
astragaloside II	glc *	H	CH_3CO	H	H
astragaloside III	H	H	glc *	H	H
astragaloside IV	glc *	H	H	H	H
astragaloside V	H	glc *	glc *	H	H
astragaloside VI	glc *	H	glc *	H	H
astragaloside VII	glc *	glc *	H	H	H
isoastragaloside I	glc *	H	CH_3CO	H	CH_3CO
isoastragaloside II	glc *	H	H	CH_3CO	H

* glc = β-D-glucopyranosyl



astragaloglucans

Dosage forms

Crude plant material; extracts. Store in a dry environment protected from moisture and insects (*1*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As adjunctive therapy in the treatment of colds and influenza (*1*). The herb is used to enhance the immune system and to increase stamina and endurance (*1*).

Also in the treatment of chronic diarrhoea, oedema, abnormal uterine bleeding, and diabetes mellitus (*1*, *4*, *14*, *15*), and as a cardiotonic agent (*6*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of nephritis, chronic bronchitis, postpartum urine retention, leprosy, and the sequelae of cerebrovascular accidents (*4*).

Pharmacology

Experimental pharmacology

Effect on the immune system

Both *in vitro* and *in vivo* investigations have confirmed that *Astragalus membranaceus* enhances the immune system (*14–18*). *In vitro* studies have shown that, at concentrations of 10 mg/ml, polysaccharides isolated from the plant increased the blastization index in mixed lymphocyte cultures and the granulopexis of macrophages or polymorphonucleates (*16*). Using the local xenogenic graft-versus-host reaction (assessed in cyclophosphamide-treated rats) as a model assay for T-cell function, investigators found that mononuclear cells, derived from cancer patients, that were preincubated with a polysaccharide fraction from *A. membranaceus* had significant immunopotentiating activity, and they fully corrected *in vitro* T-cell function deficiency found in cancer patients (*14*). Further investigations of this extract established that the polysaccharide fraction enhanced interleukin-2 activity in the *in vitro* generation of lymphokine-activated killer cell activity (*17*). Intravenous injection of this polysaccharide fraction also reversed cyclophosphamide-induced immunosuppression in rats (*18*).

A decoction of *A. membranaceus* given to mice by gastric lavage, daily or on alternate days for 1–2 weeks, increased the phagocytic activity of the reticuloendothelial system (*4*, *5*). The phagocytic index was significantly enhanced even when the rehabilitation of the mouse reticuloendothelial system was disrupted by injection of carbon particles before the *A. membranaceus* extract was administered (*4*, *5*). Extracts of the crude drug enhanced antibody response to a T-dependent antigen *in vivo*. Intravenous administration of a crude drug

extract to normal mice, or mice immunosuppressed by cyclophosphamide, radiation treatment, or ageing, induced the antibody response to a T-dependent antigen (*19*). Enhancement of this response is associated with an increase in T-helper cell activity in both normal and immunosuppressed mice (*19*). Other *in vivo* studies performed on cyclophosphamide-immunosuppressed mice have further suggested that *A. membranaceus* root extracts may modulate the immune system by activation of macrophages and splenic lymphocytes (*20*).

The immunostimulant activity of *A. membranaceus* has been associated with the polysaccharide fractions of the root extract (*4, 13, 19, 21*). The immune-enhancing polysaccharide molecules have relative molecular masses of approximately 25 000 (*14, 18, 19*). A polysaccharide fraction isolated from *A. membranaceus* reportedly antagonized the effect of cobra venom on the immune function of treated mice and guinea-pigs (*22*). The venom-treated guinea-pigs had decreased levels of complement and neutrophil phagocytotic activity, as well as increased levels of neutrophil granular substances. Treatment of the animals with the polysaccharides antagonized these changes in the venom-treated animals but had no effect in the normal group (*22*). Recently, a new glycan, named AMem-P, isolated from the roots of *A. membranaceus,* was shown by use of an *in vivo* carbon clearance test to significantly potentiate reticuloendothelial system activity in mice (*13*).

Radix Astragali is reported to have cardiovascular activity. Alcohol extracts of the drug enhanced both the contractility and contraction amplitude of isolated frog or toad hearts (*4*). Intraperitoneal injection of the drug to dogs did not produce any immediate effect on heart rate, but 3–4 hours after administration inverted and biphasic T waves and prolonged S–T intervals were noted (*4*). Intravenous administration of the drug produced hypotension in rabbits, dogs, and cats (*4*). Furthermore, saponins isolated from the drug were reported to exert a positive inotropic effect on isolated rat hearts (*23*). The saponins also decreased the resting potential of cultured rat myocardial cells, suggesting that they may exert an inotropic effect through the modulation of Na^+/K^+-exchanging ATPase (*23*).

Toxicology

No adverse effects were observed in mice after oral administration of up to 100 g/kg, a dose several hundred times as high as the effective oral dose in humans (*4*).

Clinical pharmacology

Oral or intranasal administration of an aqueous *A. membranaceus* extract to 1000 human subjects decreased the incidence and shortened the course of the common cold (*4*). Two months of oral administration of the herb significantly increased the levels of IgA and IgG in the nasal secretions of patients susceptible to the common cold (*4*). Details of these studies were not available.

A hot water extract of *A. membranaceus* root taken by human subjects was

reported to have a pronounced immunostimulant effect (*24*). Human adults treated with an oral dose of *Astragalus* root (15.6 g per person per day for 20 days) significantly increased serum IgM, IgE, and cyclic AMP concentrations (*24*). Extracts of *A. membranaceus* have been further reported to stimulate the production of interferon, a protein with antiviral activity, in both animals and humans in response to viral infections (*21*, *25*). A hot water extract of the drug administered intramuscularly for 3–4 months to patients with coxsackievirus B myocarditis enhanced natural killer cells, a response which was mediated through interferon induction (*15*). Furthermore, both natural and recombinant interferons enhanced the antiviral activity of an *A. membranaceus* extract (*26*).

Contraindications

No information available.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Extracts of *A. membranaceus* root were not mutagenic in a modified Ames test using *Salmonella typhimurium* TA 98 and TA 100 (*27*). Furthermore, an aqueous extract of *A. membranaceus* was reported to be antimutagenic in that it inhibited benzo[*a*]pyrene-induced mutagenesis in *Salmonella typhimurium* TA 100 (*28*, *29*).

Pregnancy: non-teratogenic effects

No data available; therefore Radix Astragali should not be administered during pregnancy.

Nursing mothers

Excretion of the drug into breast milk and its effects on the newborn infant have not been established; therefore the use of the drug during lactation is not recommended.

Other precautions

No information available describing general precautions or precautions related to drug interactions, drug and laboratory test interactions, paediatric use, or teratogenic effects during pregnancy.

Adverse reactions

No information available.

Posology

Root: 9–30 g/day for oral use (*1*).

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Herba Centellae

Definition

Herba Centellae consists of the dried aerial parts or the entire plant of *Centella asiatica* (L.) Urban. (Apiaceae) (*1–5*).

Synonyms

Centella coriacea Nannfd., *Hydrocotyle asiatica* L., *Hydrocotyle lunata* Lam. and *Trisanthus cochinchinensis* Lour. (*1*, *3*, *6*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Artaniyae-hindi, Asiatic pennywort, barmanimuni, barmi, bhram buti, boa-bok, bodila-ba-dinku, bokkudu, brahma manduki, brahmi ghi, brahmi-buti, brahmi, bua bok, bua-bok, centella, chhota mani-muni, chi-hsueh-ts'ao, ghi brahmi, ghod tapre, ghodtapre, ghortapre, gotu kola, gotukola, herba pegagan, herba kakikuda, hydrocotyle, hydrocotyle asiatique, idrocotile, imsen korokla, Indian pennywort, Indian water navelwort, Indischer Wassernabel, karinga, karivana, kudangal, luei gong gen, lièn tièn tháo, mandooka parni, mandukaparni, mandukparni, manimuni, marsh pepperwort, matoyahuho, matoyahuhu, mrang-khua, mtwigahuwu, pa-na-e-khaa-doh, phác chèn, phaknok, phalwaen, rau má, saraswathiaaku, takip-kohol, thalkuri, thankuni, thol-kuri, tilkushi, titjari, tono'itahi, tsubo-kusa, tungchian, vallari, vallarei, vitovitolenge, water pennywort, waternavel, yahon-yahon, yerba de chavos (*3–11*).

Description

A slender trailing herb, rooting at the nodes. Leaves 1.3–6.3 cm diameter, orbicular reniform, more or less cupped, entire, crenate or lobulate, glabrous; leaf stalks 2–5 cm long; peduncle about 6 mm, often 2–3 nates; pedicels nil; bracts small, embracing the flowers; inflorescence in single umbel, bearing 1–5 flowers, sessile, white or reddish; fruit small, compressed, 8 mm long, mericarps longer than broad, curved, rounded at top, 7–9-ridged, secondary ridges as prominent as the primary, reticulate between them; pericarp much thickened; seed compressed laterally (*1*, *4*, *7*).

Plant material of interest: aerial part or entire plant

General appearance

A slender herb. Stems long, prostrate, emerging from the leaf-axils of a vertical rootstock, filiform, often reddish, with long internodes and rooting at the nodes; leaves thin, long-petioled, several from the rootstock and 1–3 from each node of the stems, 1.3–6.3 cm diameter, orbicular reniform, more or less cupped, entire, crenate or lobulate, glabrous; petioles very variable in length, 7.5–15 cm long or more, channelled; stipules short, adnate to the petioles forming a sheathing base (*4*, *5*).

Organoleptic properties

Colour, greyish green; odour, characteristic; taste, slightly bittersweet (*4*, *5*).

Microscopic characteristics

Greyish green with stomata on both surfaces of the leaf, 30 by 28 μm, mostly rubiaceous type. Palisade cells differentiated into 2 layers of cells, 45 by 25 μm; spongy parenchyma of about 3 layers of cells with many intercellular spaces, some with crystals of calcium oxalate; midrib region shows 2 or 3 layers of parenchymatous cells without chloroplastids; petiole shows epidermis with thickened inner walls; collenchyma of 2 or 3 layers of cells; a broad zone of parenchyma; 7 vascular bundles within parenchymatous zone, 2 in projecting arms and 5 forming the central strand; vessels 15–23 μm in diameter. Some parenchymatous cells contain crystals of calcium oxalate. Fruits, epidermis of polygonal cells, trichomes similar to the leaves, sheets of elongated parquetry layer cells, bundles of narrow annular vessels, and parenchymatous cells contain single large prisms of calcium oxalate (*4*).

Geographical distribution

The plant is indigenous to the warmer regions of both hemispheres, including Africa, Australia, Cambodia, Central America, China, Indonesia, the Lao People's Democratic Republic, Madagascar, the Pacific Islands, South America, Thailand, southern United States of America, and Viet Nam. It is especially abundant in the swampy areas of India, the Islamic Republic of Iran, Pakistan, and Sri Lanka up to an altitude of approximately 700 m (*1*, *4*, *6*, *8*, *10*, *11*).

General identity tests

Macroscopic and microscopic examinations; and microchemical tests for the presence of triterpenes and reducing sugars (*1*, *4*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Herba Centellae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*12–14*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 2% (*4*).

Total ash

Not more than 19% (*2, 3*).

Acid-insoluble ash

Not less than 6% (*2*).

Water-soluble extractive

Not less than 6% (*2, 3*).

Alcohol-soluble extractive

Not less than 9.5% (*2, 3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Centellae is not more than 0.05 mg/kg (*14*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*12*) and guidelines for predicting dietary intake of pesticide residues (*15*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*12*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*12*).

Other purity tests

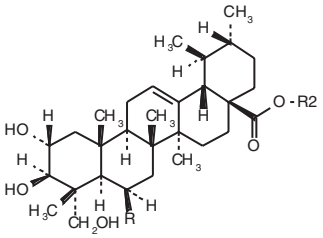
Chemical tests, and tests for drug interactions and moisture to be established by national authorities.

Chemical assays

Contains not less than 2% triterpene ester glycosides (asiaticoside and madecassoside) (*10*). Determination of asiaticoside and related triterpene ester glycosides by thin-layer chromatography (*16*) and spectroscopic analysis (*17*).

Major chemical constituents

The major principles in Herba Centellae are the triterpenes asiatic acid and madecassic acid, and their derived triterpene ester glycosides, asiaticoside and madecassoside (*8*, *10*, *11*).

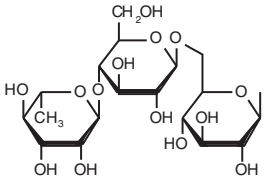


asiatic acid R1 = H , R2 = OH

madecassic acid R1 = OH , R2 = OH

rha-glc-glc- =

O-α-L-rhamnopyranosyl-(1→4)-*O*β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl
or
O-6-deoxy-α-L-mannopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl



asiaticoside R1 = H , R2 = rha-glc-glc-

madecassoside R1 = OH , R2 = rha-glc-glc-

Dosage forms

Dried drug for infusion (*18*); galenic preparations for oral administration (*10*). Powder or extract (liquid or ointment) for topical application (*1*, *4*). Package in well-closed, light-resistant containers.

Medicinal uses

Uses supported by clinical data

Treatment of wounds, burns, and ulcerous skin ailments, and prevention of keloid and hypertrophic scars (*10*, *18–21*). Extracts of the plant have been employed to treat second- and third-degree burns (*19*). Extracts have been used topically to accelerate healing, particularly in cases of chronic postsurgical and post-trauma wounds (*19*). Extracts have been administered orally to treat stress-induced stomach and duodenal ulcers (*10*).

Uses described in pharmacopoeias and in traditional systems of medicine

Herba Centellae is reported to be used in the treatment of leprous ulcers and venous disorders (*5*, *6*, *8*, *10*, *22*).

Studies suggest that extracts of *Centella asiatica* cause regression of inflammatory infiltration of the liver in cirrhosis patients (*10*, *23*). Further experimentation is needed to confirm these findings.

Uses described in folk medicine, not supported by experimental or clinical data

Therapy of albinism, anaemia, asthma, bronchitis, cellulite, cholera, measles, constipation, dermatitis, diarrhoea, dizziness, dysentery, dysmenorrhoea, dysuria, epistaxis, epilepsy, haematemesis, haemorrhoids, hepatitis, hypertension, jaundice, leukorrhoea, nephritis, nervous disorders, neuralgia, rheumatism, smallpox, syphilis, toothache, urethritis, and varices; and as an antipyretic, analgesic, anti-inflammatory, and "brain tonic" agent (*4*, *5*, *7*). Poultices have been used to treat contusions, closed fractures, sprains, and furunculosis (*7*).

Pharmacology

Experimental pharmacology

The pharmacological activity of *Centella asiatica* is thought to be due to several saponin constituents, including asiaticoside, asiatic acid, and madecassic acid (*10*). *In vitro*, each of these compounds stimulated the production of human collagen I, a protein involved in wound healing (*24*). Stimulation of collagen synthesis in foreskin fibroblast monolayer cultures by an extract from Herba Centellae has also been reported (*25*). Asiaticoside accelerated the healing of superficial postsurgical wounds and ulcers by accelerating cicatricial action (*21*). Asiaticoside stimulates the epidermis by activating the cells of the malpighian layer in porcine skin, and by keratinization *in vitro* (*26*). Topical application of asiaticoside promoted wound healing in rats and significantly increased the tensile strength of newly formed skin (*21*, *27*).

Extracts of *C. asiatica*, and in particular its major triterpene ester glycoside, asiaticoside, are valuable in the treatment of hypertrophic scars and keloids (*21*). Asiaticoside has been reported to decrease fibrosis in wounds, thus preventing new scar formation (*21*). The mechanism of action appears to be twofold: by increasing the synthesis of collagen and acidic mucopolysaccharides, and by inhibiting the inflammatory phase of hypertrophic scars and keloids. It has further been proposed that asiaticoside interferes with scar formation by increasing the activity of myofibroblasts and immature collagen (*21*).

Extract of Herba Centellae effectively treated stress-induced stomach and duodenal ulcers in humans (*10*, *28*). Oral administration of *C. asiatica* extract to rats produced a dose-dependent reduction in stress-induced gastric ulceration, and the antiulcer activity was similar to that of famotidine (*29*). The mechanism of action appears to be associated with a central nervous system-depressant activity of *C. asiatica*, owing to an increase in the concentration of GABA (γ-aminobutyric acid) in the brain (*29*).

A 70% ethanol extract of the drug administered intraperitoneally to mice produced anticonvulsant activity (*30*).

Clinical pharmacology

In clinical trials, an extract of *C. asiatica* in a 1% salve or 2% powder accelerated healing of wounds (*31*). A formulation containing asiaticoside as the main ingredient healed 64% of soiled wounds and chronic or recurrent atony that was resistant to usual treatment (*21*). In an open clinical study, treatment of 20 patients with soiled wounds and chronic or recurrent atony with a galenical formulation containing 89.5% *C. asiatica* healed 64% and produced improvement in another 16% of the lesions studied (*20*). Local application of an extract of the drug to second- and third-degree burns expedited healing, prevented the shrinking and swelling caused by infection, and further inhibited hypertrophic scar formation (*11*).

Twenty-two patients with chronic infected skin ulcers were treated with a cream containing a 1% extract of *C. asiatica* (*32*). After 3 weeks of treatment, 17 of the patients were completely healed and the ulcer size in the remaining 5 patients was decreased (*32*). Another trial using the same cream preparation demonstrated similar results (*33*). A standardized extract of Herba Centellae was reported to treat ulcus cruris (indolent leg ulcers) effectively in clinical trials (*34, 35*). In a double-blind study, no significant effect on healing was observed in patients with ulcus cruris after oral treatment with asiaticoside (*36*).

Oral administration of *C. asiatica* or asiaticoside and potassium chloride capsules was reported to be as effective as dapsone therapy in patients with leprosy (*37*). In a controlled study of 90 patients with perforated leg lesions owing to leprosy, application of a salve of the plant produced significantly better results than a placebo (*11, 22, 38*).

Clinical trials of the drug have demonstrated its antiulcer activity after oral administration (*28, 39, 40*). Fifteen patients with peptic or duodenal ulcer were treated with a titrated extract of Herba Centellae (60.0 mg/person). Approximately 93% of the patients exhibited a definite improvement in subjective symptoms and 73% of the ulcers were healed as measured by endoscopic and radiological observations (*28*).

Clinical studies of Herba Centellae in the treatment of various venous disorders has demonstrated a positive therapeutic effect (*11*). In patients suffering from venous insufficiency who were treated with a titrated extract of the drug, venous distension and oedema improved significantly, as compared with controls (*41*).

Contraindications

Allergy to plants of the Apiaceae family.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Asiaticoside has been implicated as a possible skin carcinogen in rodents after repeated topical application (*42*). Further experimentation is needed to substantiate this claim.

Other precautions

No information was available concerning drug interactions, drug and laboratory test interactions, teratogenic or non-teratogenic effects on pregnancy, nursing mothers, or paediatric use.

Adverse reactions

Allergic contact dermatitis has been associated with topical application of *C. asiatica* (*21*, *43*, *44*). However, further testing revealed that these reactions may be due to other ingredients in the preparations (*45*).

Posology

Oral dose: 0.33–0.68 g or by oral infusion of a similar amount three times daily (*4–6*).

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Flos Chamomillae

Definition

Flos Chamomillae consists of the dried flowering heads of *Chamomilla recutita* (L.) Rauschert (Asteraceae) (*1–4*).

Synonyms

Matricaria chamomilla L., *M. recutita* L., *M. suaveolens* L. (3).

In most formularies and reference books, *Matricaria chamomilla* L. is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Chamomilla recutita* (L.) Rauschert is the legitimate name for this species (*5*). Asteraceae are also known as Compositae.

Selected vernacular names

Baboonig, babuna, babunah camomile, babunj, bunga kamil, camamilla, camomile, chamomile, camomilla, chamomille allemande, campomilla, chamomille commune, camomille sauvage, fleurs de petite camomille, flos chamomillae, german chamomile, hungarian chamomile, Kamille, Kamillen, kamitsure, kamiture, manzanilla, manzanilla chiquita, manzanilla comun, manzanilla dulce, matricaire, matricaria flowers, pin heads, sweet false chamomille, sweet feverfew, wild chamomile (3, *6–9*).

Description

Herbaceous annual; 10–30 cm in height, with erect, branching stems and alternate, tripinnately divided leaves below and bipinnately divided leaves above, both types having almost filiform lobes; the capitulum (to 1.5 cm in diameter) comprises 12–20 white ligulate florets surrounding a conical hollow receptacle on which numerous yellow tubular (disk) florets are inserted; the inflorescence is surrounded by a flattened imbricated involucre; fruit small, smooth, yellowish (3, *7*, *10*).

Plant material of interest: flower heads

General appearance

Flos Chamomillae consists of conical flower heads, each bearing a few white ligulate florets and numerous yellowish orange to pale yellow tubular or disk florets on conical, narrow hollow receptacles with a short peduncle; disk florets

perfect and without a pappus; ray florets pistillate, white, 3-toothed and 4-veined; involucre hemispherical, composed of 20–30 imbricate, oblanceolate and pubescent scales; peduncles weak brown to dusky greenish yellow, longitudinally furrowed, more or less twisted and up to 2.5 cm long; achenes more or less obovoid and faintly 3- to 5-ribbed; pappus none, or slightly membranous crown (*7*, *11*).

Organoleptic properties

Odour, pleasant, aromatic; taste, aromatic and slightly bitter (*1*–*3*).

Microscopic characteristics

Receptacle and bracteoles with schizogenous secretory ducts; vascular bundles with phloem fibres; spiral, annular and reticulate but pitted vessels; lignified cells at the bases of the ovaries absent; nearly all parts of florets bear composite-type glandular hairs with short, biseriate stalk and enlarged head, formed of several tiers, each of two cells; ovary with longitudinal bands of small mucilage cells; stigma with elongated papillae at the apex; pollen grains, spherical or triangular, with numerous short spines (*3*).

Powdered plant material

Powdered Flos Chamomillae is greenish yellow to yellowish brown; spiny pollen grains numerous, 18–25 µm in diameter; fragments of yellow or white corolla, with polygonal, small epidermal cells having straight or slightly wavy walls, sometimes papillosed, and sometimes bearing glandular hairs of composite type; fragments of the fibrous layer of anther; fragments from ovary, with glandular hairs and rows of small mucilage cells; green fragments of parenchyma of involucre; stigma with papillae; cells of the achenes with sclariform perforations in walls; fragments of fibrovascular bundles with spiral, annular and reticulate vessels and sclerenchyma fibres; fragments of involucral bracts with epidermis having elliptical stomata up to 30 µm in length, also vessels and fibres; occasional fibre from the stems; minute cluster crystals of calcium oxalate, up to 10 µm in diameter; fragments of lignified parenchyma of the filaments and occasional fragments of vessels (*3*, *7*, *10*).

Geographical distribution

The plant is indigenous to northern Europe and grows wild in central European countries; it is especially abundant in eastern Europe. Also found in western Asia, the Mediterranean region of northern Africa, and the United States of America. It is cultivated in many countries (*3*, *7*–*13*).

General identity tests

The drug is identified by its macroscopic and microscopic characteristics, and by thin-layer chromatography (*1*–*3*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Flos Chamomillae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*1*, *14*, *15*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml. Preparations for external use: aerobic bacteria—not more than 10^2/g or ml; fungi—not more than 10^2/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^1/g or ml.

Foreign organic matter

Not more than 10% stems and not more than 2% foreign organic matter (*3*). No flowering heads of *Anthemis cotula* L. or *A. nobilis* L. (*7*).

Total ash

Not more than 13% (*2*).

Acid-insoluble ash

Not more than 4% (*11*).

Moisture

Not more than 12% (*12*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Flos Chamomillae is not more than 0.05 mg/kg (*1*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*14*) and guidelines for predicting dietary intake of pesticide residues (*16*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*14*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*14*).

Other tests

Chemical, dilute ethanol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

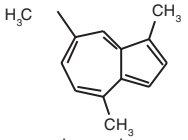
Chemical assays

Contains not less than 0.4% v/w of essential oil (*1–3*). Total volatile oil content is determined by pharmacopoeial methods (*1–3*).

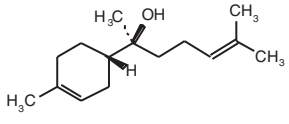
Thin-layer (*1, 2*) and gas–liquid (*17*) chromatography for volatile oil constituents, and high-performance liquid chromatography for flavonoids (*18, 19*).

Major chemical constituents

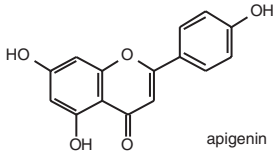
Flos Chamomillae contains an essential oil (0.4–1.5%), which has an intense blue colour owing to its chamazulene content (1–15%). Other major constituents include α-bisabolol and related sesquiterpenes (up to 50% of the oil). Apigenin and related flavonoid glycosides constitute up to 8% (dry weight) of the drug (*10, 18*).



chamazulene



(−)-α-bisabolol



apigenin

Dosage forms

Dried flower-heads, liquid extract (1:1 in 45% alcohol), tinctures and other galenicals (*11*). Store in well-closed containers, protected from light (*1–3*).

Medicinal uses

Uses supported by clinical data

Internal use

Symptomatic treatment of digestive ailments such as dyspepsia, epigastric bloating, impaired digestion, and flatulence (*3, 7, 8, 10, 11, 20, 21*). Infusions of camomile flowers have been used in the treatment of restlessness and in mild cases of insomnia due to nervous disorders (*21, 22*).

External use

Inflammation and irritations of the skin and mucosa (skin cracks, bruises, frostbite, and insect bites) (*10, 23*), including irritations and infections of the mouth and gums, and haemorrhoids (*10, 11, 20, 21, 23*).

Inhalation

Symptomatic relief of irritations of the respiratory tract due to the common cold (*24*).

Uses described in pharmacopoeias and in traditional systems of medicine

Adjuvant in the treatment of minor inflammatory conditions of the gastrointestinal tract (*24*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antibacterial and antiviral agent, an emetic, and an emmenagogue. It is also used to relieve eye strain, and to treat urinary infections and diarrhoea (*13*).

Pharmacology

Experimental pharmacology

Both camomile extract and (−)-α-bisabolol demonstrated antipeptic activity *in vitro* (*25*, *26*). A hydroalcoholic extract of camomile inhibited the growth of *Staphylococcus aureus, Streptococcus mutans*, group B *Streptococcus*, and *Streptococcus salivarius*, and it had a bactericidal effect *in vitro* on *Bacillus megatherium* and *Leptospira icterohaemorrhagiae* (*27*). *In vitro*, the volatile oil of camomile also inhibited *Staphylococcus aureus* and *Bacillus subtilis* (*28*). *In vitro*, camomile extracts inhibited both cyclooxygenase and lipoxygenase (*29*), and thus the production of prostaglandins and leukotrienes, known inducers of inflammation. Both bisabolol and bisabolol oxide have been shown to inhibit 5-lipoxygenase, but bisabolol was the more active of the two compounds (*30*). Numerous *in vivo* studies have demonstrated the anti-inflammatory effects of the drug. The anti-inflammatory effects of camomile extract, the essential oil, and the isolated constituents have been evaluated in yeast-induced fever in rats and against ultraviolet radiation-induced erythema in guinea-pig models (*31*). The principal anti-inflammatory and antispasmodic constituents of camomile appear to be the terpene compounds matricin, chamazulene, (−)-α-bisabololoxides A and B, and (−)-α-bisabolol (*32*–*39*). While matricin and (−)-α-bisabolol have been isolated from the plant, chamazulene is actually an artefact formed during the heating of the flowers when an infusion or the essential oil is prepared (*10*). The anti-inflammatory effects of these compounds in various animal models, such as inhibition of carrageenin-induced rat paw oedema, have been demonstrated (*30*), although their activity was somewhat less than that of salicylamide (*39*). In the mouse model for croton oil-induced dermatitis, topical application of either the total camomile extract, or the flavonoid fraction only, was very effective in reducing inflammation (*34*). Apigenin and luteolin were more active than indometacin and phenylbutazone (*34*). Activity decreased in the following

order: apigenin > luteolin > quercetin > myricetin > apigenin-7-glucoside > rutin (*34*). The spasmolytic activity of camomile has been attributed to apigenin, apigenin-7-*O*-glucoside (*10*, *36*) and (−)-α-bisabolol, which have activity similar to papaverine (*10*, *35*).

Intradermal application of liposomal apigenin-7-glucoside inhibited, in a dose-dependent manner, skin inflammations induced in rats by xanthine oxidase and cumene hydroperoxide (*38*).

Intraperitoneal administration to mice of a lyophilized infusion of camomile decreased basal motility, exploratory and motor activities, and potentiated hexobarbital-induced sleep (*40*). These results demonstrated that in mice camomile depresses the central nervous system (*40*).

Clinical pharmacology

A double-blind study of the therapeutic effects of a camomile extract on re-epithelialization and drying of wound weeping after dermabrasion demonstrated a statistically significant decrease in the wound size and drying tendency (*41*).

In clinical trials, topical application of a camomile extract in a cream base was found to be superior to hydrocortisone 0.25% for reducing skin inflammation (*42*). In an international multicentre trial camomile cream was compared with hydrocortisone 0.25%, fluocortin butyl ester 0.75% and bufexamac 5% in the treatment of eczema of the extremities (*42*). The camomile cream was shown to be as effective as hydrocortisone and superior to the other two treatments, but no statistical analysis was performed. Camomile preparations have also been found to be beneficial in the treatment of radiation mucositis owing to head and neck radiation and systemic chemotherapy (*43*).

Contraindications

Camomile is contraindicated in patients with a known sensitivity or allergy to plants of the Asteraceae (Compositae) such as ragweed, asters, and chrysanthemums (*21*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No mutagenic effects were found in *Salmonella typhimurium* strains TA 97a, TA 98, TA 100 and TA 104, with or without metabolic activation (*44*).

Pregnancy: teratogenic effects

No adverse effects reported *in vivo* (*45*).

Other precautions

No information available concerning general precautions, drug interactions, drug and laboratory test interactions, non-teratogenic effects on pregnancy, nursing mothers, or paediatric use.

Adverse reactions

The presence of lactones in Flos Chamomillae-based preparations may cause allergic reactions in sensitive individuals and there have been reports of contact dermatitis due to camomile preparations (*46–48*). It should be noted that very few cases of allergy were specifically attributed to German camomile (*49*). A few cases of anaphylactic reactions to the ingestion of Flos Chamomillae have also been reported (*50–52*).

Posology

Internal use

Adult dose of flower head: average daily dose 2–8 g, 3 times a day (*7*, *8*, *11*); of fluid extract 1 : 1 in 45% ethanol: dose 1–4 ml, 3 times a day (*6*, *11*). Child dose of flower head: 2 g, 3 times daily; of fluid extract (ethanol 45–60%): single dose 0.6–2 ml (*11*). Should not be used by children under 3 years old.

External use

For compresses, rinses or gargles: 3–10% (30–100 g/l) infusion or 1% fluid extract or 5% tincture (*11*). For baths: 5 g/l of water or 0.8 g/l of alcoholic extract. For semisolid preparations: hydroalcoholic extracts corresponding to 3–10% (30–100 g/kg) of the drug. For vapour inhalation: 6 g of the drug or 0.8 g of alcoholic extract per litre of hot water (*11*).

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Cortex Cinnamomi

Definition

Cortex Cinnamomi consists of the dried inner bark of the shoots grown on cut stock of *Cinnamomum verum* J.S. Presl. (*1–5*) or of the trunk bark, freed of cork, of *Cinnamomum cassia* Blume (*6–8*) (Lauraceae).

Synonyms

Cinnamomum verum J.S. Presl.

Cinnamomum zeylanicum Nees (*9–11*), *Laurus cinnamomum* L. (*4*).

Cinnamomum verum J.S. Presl. is the correct botanical name according to the International Rules of Botanical Nomenclature (*11*).

Cinnamomum cassia Blume

Cinnamomum aromaticum Nees (*7, 12, 13*).

Selected vernacular names

Cinnamomum verum J.S. Presl.

Abdalasini, blood-giving drops, canela, canela en raja, cannalavanga pattai, cannelle de ceylan, cannelle dite de Ceylan, cannelier, Ceylon celonzimi cinnamon, Ceylon cinnamon, cinnamon, cinnamon bark, cinnamon tree, cortex cinnamomi ceylanici, dalchini, dalochini, dar sini quirfa, darchini, daruchini, darusila, ecorce de cannelier de Ceylan, echter Kanel, gujerati-dalchini, kannel, kuei-pi, kurundu, kurundu-potu, kulit kayumanis, ob choei, tamalpatra, wild cinnamon, Zimtrinde (*2–4, 10, 14, 15*).

Cinnamomum cassia Blume

Annan cinnamon, cassia, cassia bark, cassia bark tree, cassia lignea, chinazimt, Chinese cassia, Chinese cinnamon, ching hua yu-kuei, cinnamomi cassiae cortex, cinnamon, cinnamon bark, dalchini, guipi, guizhi, kannan keihi, keihi, keishi, kuei-chíi, lavanga-pattai, lavanga-patti, lurundu, macrophyllos cassia bark tree, rou gui, róugì, Saigon cinnamon, saleekha, taj, toko keihi, Viet Nam cinnamon (*6, 7, 12–17*).

Description

Cinnamomum verum J.S. Presl.

A moderate-sized evergreen tree; bark rather thick, smooth, pale; twigs often compressed; young parts glabrous except the buds which are finely silky. Leaves opposite or subopposite (rarely alternate), hard and coriaceous, 7.5–20 by 3.8–7.5 cm, ovate or ovate-lanceolate, subacute or shortly acuminate, glabrous and shining above, slightly paler beneath, base acute or rounded; main nerves 3–5 from the base or nearly so, strong, with fine reticulate venation between; petioles 1.3–2.5 cm long, flattened above. Flowers numerous, in silky pubescent, lax panicles usually longer than the leaves; peduncles long, often clustered, glabrous or pubescent; pedicels long. Perianth 5–6 mm long; tube 2.5 mm long; segments pubescent on both sides, oblong or somewhat obovate, usually obtuse. Fruit 1.3–1.7 cm long, oblong or ovoid-oblong, minutely apiculate, dry or slightly fleshy, dark purple, surrounded by the enlarged campanulate perianth that is 8 mm in diameter (*14*).

Cinnamomum cassia Blume

An evergreen tree, up to 10 m high. Leaves alternate, coriaceous, petiolate, oblong, elliptical-oval or oblong-lanceolate, 8–15 cm long by 3–4 cm wide, tip acuminate, base rounded, entire, 3-nerved; glabrous or underside lightly pubescent; petiole 10 mm long, lightly pubescent. Inflorescence a densely hairy panicle as long as the leaves; panicles cymose, terminal and axillary. Flowers yellowish white, small, in cymes of 2–5. Perianth 6-lobed. No petals. Stamens 6, pubescent. Ovary free, 1-celled. Fruit a globular drupe, 8 mm long, red. The bark is used in either channelled pieces or simple quills, 30–40 cm long by 3–10 cm wide and 0.2–0.8 cm in thickness. The surface is greyish brown, slightly coarse, with irregularly fine wrinkles and transverse lenticels. Here and there are found scars of holes, indicating the insertion of leaves or lateral shoots; the inner surface is rather darker than the outer, with fine longitudinal striae. The fracture is short, the section of the thicker pieces showing a faint white line (pericyclic sclerenchyma) sometimes near the centre, sometimes near and parallel to the outer margin (*14*).

Plant material of interest: dried bark, free from the outer cork

General appearance

Cinnamomum verum J.S. Presl.

The bark is about 0.2–0.8 mm thick and occurs in closely packed compound quills made up of single or double quills. The outer surface is smooth, yellowish brown with faint scars marking the positions of leaves and axillary buds and has fine, whitish and wavy longitudinal striations. The inner surface is slightly darker and longitudinally striated. The fracture is short and fibrous (*1*).

***Cinnamomum cassia* Blume**

The drug is channelled or quilted, 30–40 cm long, 3–10 cm in diameter, 2–8 mm thick. Outer surface greyish brown, slightly rough, with irregular fine wrinkles and transverse raised lenticels, some showing greyish white streaks; inner surface reddish brown, with fine longitudinal striations and exhibiting oily trace on scratching. Texture hard and fragile, easily broken, fracture uneven, outer layer brown and relatively rough, inner layer reddish brown and oily and showing a yellowish brown line between two layers (*6*).

Organoleptic properties

Odour, characteristic and aromatic (*2, 3, 4, 6*); taste, characteristic, slightly sweet and fragrant (*3, 4, 6*).

Microscopic characteristics

***Cinnamomum verum* J.S. Presl.**

The outside shows a few discontinuous layers of cortical parenchyma within which is a wide, continuous layer of pericyclic sclerenchyma composed of groups of isodiametric or tangentially elongated sclereids with thickened and pitted walls, and occasional groups of fibres. The phloem is composed of sieve tissue and parenchyma with large secretion cells containing essential oil or mucilage and phloem fibres occurring singly or in small groups, individual fibres 15–25 μm in diameter with thickened walls; medullary rays uniseriate or biseriate. Some of the cells contain small acicular crystals of calcium oxalate; the remainder, together with the phloem parenchyma, contain starch granules, simple or 2–4 compound, rarely more than 10 μm in diameter (*1, 3*).

***Cinnamomum cassia* Blume**

The transverse section shows the cork being composed of several layers of cells, the innermost layer with thickened and lignified outer walls. Cortex scattered with stone cells and secretory cells. Pericycle stone cells in groups arranged in an interrupted ring, accompanied by fibre bundles at outer side, the outer walls of stone cells usually thinner. Phloem rays 1 or 2 rows of cells wide, containing minute needle crystals of calcium oxalate; usually 2 or 3 fibres in bundles; oil cells scattered throughout. Parenchymatous cells contain starch granules (*6*).

Powdered plant material

***Cinnamomum verum* J.S. Presl.**

The powdered drug is yellowish to reddish brown and consists of groups of rounded sclereids with pitted, channelled and moderately thickened walls; numerous colourless fibres, often whole with narrow lumen and thickened, lignified walls and few pits; rarely small acicular crystals of calcium oxalate; abundant starch granules. Cork fragments are absent or very rare (*1, 3*).

***Cinnamomum cassia* Blume**

Reddish brown. Most fibres singly scattered, long fusiform, 195–920 μm long, up to 50 μm in diameter, with thickened and lignified wall, pits indistinct. Stone cells subsquare or sub-rounded, 32–88 μm in diameter, the walls thickened, some thin at one side. Oil cells sub-rounded or oblong, 45–108 μm in diameter. Needle crystals minute, scattered in ray cells. Cork cells polygonal, containing reddish brown contents (*1*).

Geographical distribution

Cinnamomum verum J.S. Presl.

Native to India and Sri Lanka (*4*, *11*, *14*); cultivated in parts of Africa, south-eastern India, Indonesia, the Seychelles, South America, Sri Lanka, and the West Indies (*4*, *10*, *11*).

Cinnamomum cassia Blume

Found in China, Indonesia, the Lao People's Democratic Republic, and Viet Nam, (*12*, *13*, *16*); mostly cultivated (*12*).

General identity tests

Macroscopic and microscopic examinations (*1–6*); and thin-layer chromatographic analysis for the presence of cinnamaldehyde (*1–6*, *8*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Cortex Cinnamomi products should be negative.The maximum acceptable limits of other microorganisms are as follows (*18–20*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

C. verum: not more than 2% (*4*, *14*). *C. cassia*: not more than 1% (*16*).

Total ash

C. verum: not more than 6% (*2*). *C. cassia*: not more than 5% (*6*, *8*, *14*, *16*).

Acid-insoluble ash

C. verum: not more than 4% (*4*). *C. cassia*: not more than 2% (*14*, *16*).

Sulfated ash

C. verum: not more than 6% (*1*, *3*). *C. cassia*: to be established in accordance with national requirements.

Alcohol (90%)-soluble extractive

C. verum: 14–16% (*4*). *C. cassia*: to be established in accordance with national requirements.

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Cortex Cinnamomi is not more than 0.05 mg/kg (*21*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*18*) and guidelines for predicting dietary intake of pesticide residues (*20*).

Arsenic and heavy metals

Recommended lead and cadmium levels are not more than 10 mg/kg and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*18*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*18*).

Other tests

Chemical tests to be established in accordance with national requirements.

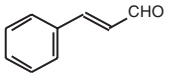
Chemical assays

Not less than 1.2% v/w of volatile oil derived from C. *verum* (*1*–*3*) and 1–2% v/w of volatile oil derived from C. *cassia* (*16*), containing 60–80% w/w aldehydes calculated as cinnamaldehyde (*3*, *16*).

Assay for cinnamaldehyde content by means of thin-layer (*1*–*4*, *6*) or high-performance liquid chromatographic (*21*, *22*) methods.

Major chemical constituents

The major constituent in both *C. verum* and *C. cassia* is cinnamaldehyde, at concentrations of 65–80% (*9*, *10*) and 90% (*9*) of the volatile oil, respectively.



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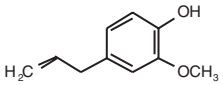
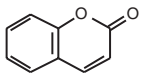


eugenol



coumarin

Cinnamomum verum also contains *o*-methoxycinnamaldehyde (*10*). *Cinnamomum verum* differs from *C. cassia* in its eugenol and coumarin content. *Cinnamomum verum* volatile oil contains 10% eugenol, whereas in *C. cassia*, only a trace quantity of this compound is found (*9*). Coumarin is present in *C. cassia* (0.45%), but not in *C. verum* (*21*).

Dosage forms

Crude plant material, powder, volatile oil, other galenic preparations. Store in a well-closed glass or metal container (do not use plastic), protected from light and moisture (*1–6*, *10*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

The treatment of dyspeptic conditions such as mild spastic conditions of the gastrointestinal tract, fullness and flatulence, and loss of appetite (*4*, *6*, *7*, *12*). Also used to treat abdominal pain with diarrhoea, and pain associated with amenorrhoea and dysmenorrhoea (*6*, *12*).

Uses described in folk medicine, not supported by experimental or clinical data

The treatment of impotence, frigidity, dyspnoea, inflammation of the eye, leukorrhoea, vaginitis, rheumatism, neuralgia, wounds, and toothache (*15*).

Pharmacology

Experimental pharmacology

Antibacterial and antifungal activities of the essential oil have been demonstrated *in vitro* (*10*). The essential oil of *C. verum* is active *in vitro* against the following bacteria: *Bacillus subtilis* (*23*, *24*), *Escherichia coli*, *Staphylococcus aureus* (*24*, *25*), *Salmonella typhimurium* (*26*), and *Pseudomonas aeruginosa* (*24*). It was also active *in vitro* against the following fungi: *Aspergillus* spp., *Cladosporium werneckii* (*27*), *Geotrichum candidum*, *Kloeckera apivulata*, *Candida lipolytica* and *C. albicans* (*23*, *28*). The antibacterial and fungicidal effects have been attributed to *o*-methoxycinnamaldehyde (*9*).

The essential oil of *C. verum* has carminative activity (*29*) and decreases smooth muscle contractions in guinea-pig trachea and ileum (*30*), and in dog ileum, colon and stomach (*31*). The active antispasmodic constituent of the drug is cinnamaldehyde. A reduction of stomach motility in rats and dogs and

intestinal motility in mice and a decrease in the number of stress- and serotonin-induced ulcers in mice have been described (*32–36*). An ethanol extract of the drug inhibits histamine- and barium-induced contractions in guinea-pig ileum; the hot-water extract was not active (*36*).

Contraindications

The drug is contraindicated in cases of fever of unknown origin, pregnancy, stomach or duodenal ulcers (*7*, *9*, *12*), and in patients with an allergy to cinnamon or Peru balsam (*9*).

Warnings

No information available.

Precautions

Drug interactions

Cinnamomum cassia bark extract (2 g in 100 ml) markedly decreased the *in vitro* dissolution of tetracycline hydrochloride (*37*). In the presence of *C. cassia* bark, only 20% of tetracycline was in solution after 30 minutes, in contrast to 97% when only water was used (*37*). However, the clinical significance of this interaction has not been established. The drug is reported to be incompatible with *Halloysitum rubrum* (*6*).

Carcinogenesis, mutagenesis, impairment of fertility

There are insufficient data to evaluate the carcinogenic potential of Cortex Cinnamomi (*35*). Reports concerning the mutagenicity of the drug are contradictory. Extracts of the plant and cinnamaldehyde have been reported to be both mutagenic and non-mutagenic in *Salmonella typhimurium* (Ames assay) and in assays using *Bacillus subtilis* (*38*, *39*). However, the results of these *in vitro* mutagenicity studies are difficult to assess because, at the doses given, the effects may have been due to the antimicrobial effects of the drug (*35*). Cortex Cinnamomi and cinnamaldehyde gave positive results in chromosomal aberration tests using Chinese hamster cell cultures (*35*), and in *Drosophila* test systems (*40–43*). An aqueous extract of the drug was also negative in the *Drosophila* test system (*35*).

Pregnancy: teratogenic effects

Available data are not sufficient for an adequate benefit/risk assessment. Therefore, Cortex Cinnamomi should not be used during pregnancy. There is one report of teratogenicity of cinnamaldehyde in chick embryos (*35*), but studies of teratogenicity in chick embryos are of limited usefulness when evaluating the teratogenic potential for humans (*35*). A methanol extract of the drug given by gastric intubation was not teratogenic in rats (*44*, *45*).

Pregnancy: non-teratogenic effects

Cortex Cinnamomi should not be used during pregnancy. See Contra-indications.

Nursing mothers

Available data are not sufficient for an adequate benefit/risk assessment. Therefore, Cortex Cinnamomi should not be used during lactation.

Paediatric use

The safety and efficacy of the drug in children have not been established.

Other precautions

No information available concerning general precautions, or drug and laboratory test interactions.

Adverse reactions

Allergic reactions of the skin and mucosa have been reported (*7*, *46–49*).

Posology

Crude drug—average daily dose, 2–4 g (*7*); volatile oil—average daily dose, 0.05–0.2 g (*7*); other preparations—average daily dose as above (*7*).

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Rhizoma Coptidis

Definition

Rhizoma Coptidis is the dried rhizome of *Coptis chinensis* Franch, *Coptis deltoides* C.Y. Cheng et Hsiao, *Coptis japonica* Makino (Ranunculaceae), or other berberine-containing species of the same genus (*1*, *2*).

Synonyms

None.

Selected vernacular names

Coptis chinensis Franch

Chinese goldthread, ch'uan-lien, coptis, coptis rhizome, gold thread, huang lian, huang-lien, huánglián, oren, Perlenschnur, weilian (*1–6*).

Coptis deltoides C.Y. Cheng et Hsiao

Coptis, gold thread, huang lian, huang-lien, huánglián, yalian (*1*, *4*, *7*).

Coptis japonica Makino

Coptis, coptis rhizome, oren (*2*, *5*).

Description

Coptis chinensis Franch

A perennial stemless herb, 20–50 cm high. Leaves basal, long petiolate; blade triangular-ovate, 3–8 cm long by 2.5–7 cm wide, ternatisect; leaflets pinnatifid, lobes incised, the terminal leaflet longer than the others. Peduncles 1–2, 12–25 cm long, bracts resembling leaves. Inflorescence a terminal cyme with 3–8 whitish green flowers; sepals narrow-ovate, 9–12 mm long; petals small, oblanceolate, 5–7 mm long; stamens numerous, 3–6 mm long; carpels 8–12, with carpophores, follicles many-seeded. Seeds with black crustaceous testa. Rhizome shaped like a cockspur, 5–6 cm long, brownish yellow, densely covered with numerous nodes and often with rootlets; interior yellow-orange; in transverse section, the central pith deeper in colour (*4*).

Coptis deltoides C.Y. Cheng et Hsiao and Coptis japonica Makino

Descriptions to be established by appropriate national authorities.

Plant material of interest: dried rhizome

General appearance

Coptis chinensis Franch

The rhizome is curved, gathered in a cluster and resembles "chicken feet", 3–6 cm long and 3–8 mm in diameter. Rough, greyish yellow or yellowish brown surface, bearing irregular protrusions, rootlets, and rootlet remnants. Apex often bearing remains of stem or petiole. Texture is hard and fracture uneven. Bark is orange-red or dark brown; wood brightly yellow or orange-yellow. Pith, sometimes hollowed (*1*).

Coptis deltoides C.Y. Cheng et Hsiao

Frequently single, somewhat cylindrical, slightly curved, 4–8 cm long and 0.5–1 cm in diameter. Internodes smooth and relatively long. Apex with some stem remains (*1*).

Coptis japonica Makino

Irregular, cylindrical rhizome, 2–4 cm, rarely up to 10 cm in length, 0.2–0.7 cm in diameter, slightly curved and often branched; externally greyish yellow-brown, with ring nodes, and with numerous remains of rootlets; generally remains of petiole at one end; fractured surface rather fibrous; cork layer light greyish brown, cortex yellow-brown, xylem yellow, and pith yellow-brown in colour (*2*).

Organoleptic properties

Odour, slight; taste, very bitter; colour, greyish yellow to yellowish brown, drug when chewed colours saliva yellow (*1*, *2*).

Microscopic characteristics

Coptis chinensis Franch

In transverse section cork cells occupy several layers. Cortex broader than others; stone cells singly or grouped together; pericycle fibres yellow, in bundles or accompanied by stone cells; collateral vascular bundles arranged in a ring. Interfascicular cambium indistinct. Xylem yellow, lignified with well developed fibres. Pith consisting of parenchyma cells and devoid of stone cells (*1*).

Coptis deltoides C.Y. Cheng et Hsiao

Transverse section shows pith with stone cells (*1*).

Coptis japonica Makino

Transverse section reveals a cork layer composed of thin-walled cork cells; cortex parenchyma usually contains groups of stone cells near the cork layer and yellow phloem fibres near the cambium; xylem consists chiefly of vessels, tracheae and wood fibres; medullary ray distinct; pith large; in pith, stone cells or sometimes stone cells with thick and lignified cells are recognized; parenchyma cells contain minute starch grains (*2*).

Powdered plant material

Coptis japonica Makino

Almost all elements are yellow. The powder shows mainly fragments of vessels, tracheids, and xylem fibres; parenchyma cells containing starch grains; polygonal cork cells. Usually, round to obtuse polygonal stone cells and their groups, and phloem fibres, 10–20 μm in diameter, and fragments of their bundles. Occasionally, polygonal and elongated epidermal cells, originating from the petiole, having characteristic thickened membranes. Starch grains are single grains 1–7 μm in diameter (*2*).

Coptis chinensis Franch and *Coptis deltoides* C.Y. Cheng et Hsiao

Descriptions to be established by appropriate national authorities.

Geographical distribution

Coptis chinensis Franch. and Coptis deltoides C.Y. Cheng et Hsiao

China (*3*, *4*).

Coptis japonica Makino

Japan (*2*).

Coptis teeta Wall.

Indigenous in India, where it is considered an endangered species (*7*). *Coptis teeta* Wall. has compendial status in China (*1*), where it is cultivated commercially (*2*).

General identity tests

Macroscopic, microscopic, and microchemical examinations; thin-layer chromatographic analysis for the presence of berberine (*1*, *2*).

Purity tests

Microbiological

The test for *Salmonella* spp. in Rhizoma Coptidis products should be negative. The maximum acceptable limits of other microorganisms are as follows (*8–10*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 5.0% (*1*, *2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Rhizoma Coptidis is not more than 0.05 mg/kg (*10*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*8*) and guidelines for predicting dietary intake of pesticide residues (*11*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*8*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*8*).

Other purity tests

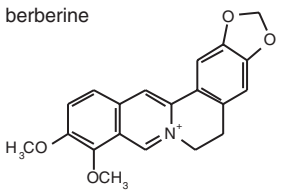
Chemical tests and tests for acid-insoluble ash, dilute ethanol-soluble extractive, foreign organic matter, moisture and water-soluble extractive are to be established in accordance with national requirements.

Chemical assays

Should contain not less than 4.2% of berberine, calculated as berberine chloride, assayed by means of thin-layer chromatography or high-performance liquid chromatography (*2*).

Major chemical constituents

The major constituents are berberine and related protoberberine alkaloids (*3*, *8*, *10*). Berberine occurs in the range of 4–8% (*C. chinensis*: 5–7%; *C. deltoides*: 4–



8%; *C. japonica*: 7–9%), followed by palmatine (*C. chinensis*: 1–4%; *C. deltoides*: 1–3%; *C. japonica*: 0.4–0.6%), coptisine (*C. chinensis*: 0.8–2%; *C. deltoides*: 0.8–1%; *C. japonica*: 0.4–0.6%), berberastine (*C. chinensis*: 1%; *C. deltoides*: 1%; *C. japonica*: trace) among others (*12*).

Dosage forms

Crude plant material, decoction, and powder. Store in a well-ventilated dry environment protected from light (*1*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

To manage bacterial diarrhoeas (*1, 4*). The drug is also used in the treatment of acute conjunctivitis, gastroenteritis, boils, and cutaneous and visceral leishmaniasis ("oriental sore") (*1, 4, 13, 14*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of arthritis, burns, diabetes, dysmenorrhoea, toothache, malaria, gout, and renal disease (*13*).

Pharmacology

Experimental pharmacology

Numerous reports support the antimicrobial activity of Rhizoma Coptidis. *In vitro* studies have shown that the crude drug and its active constituent, berberine, have a similar spectrum of antibacterial action (*3, 15*). Both inhibit the *in vitro* growth of staphylococci, streptococci, pneumococci, *Vibrio cholerae*, *Bacillus anthracis,* and *Bacillus dysenteriae*, but they do not inhibit *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhi*, *S. paratyphi*, *Pseudomonas aeruginosa,* and *Shigella sonnei* (*3*). Berberine was also active *in vitro* against *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis* (*16*).

In vitro studies have demonstrated that *V. cholerae* can grow in a medium containing berberine, but it fails to produce toxins (*17*). It has been hypothesized that the antidysenteric activity of berberine is due to local effects on the intestinal tract and not due to its bactericidal activity. The mechanism by which berberine exerts its antidiarrhoeal effects is thought to be activation of α_2-adrenoceptors and inhibition of cyclic AMP accumulation (*18*), which in turn decrease intestinal motility (*19*). However, *in vitro* studies of the drug on guinea-pig ileum contractility have demonstrated that berberine (≥1 μmol/l) inhibits acetylcholinesterase, which decreases the breakdown of acetylcholine and increases the contractility of the ileum (*20*). This study suggests that the antidiarrhoeal activity of berberine may be due to its antisecretory (*21*) as well as its antimicrobial actions (*20*). Berberine inhibits *in vivo* and *in vitro* intestinal secretions induced by cholera toxin (*22–24*). In addition, berberine reduces intestinal secretion induced by the heat-labile toxin of *Escherichia coli* in rabbit ileal loop by 70% and it markedly inhibits the secretory response of the heat-stable toxin of *E. coli* in rats (*25*, *26*).

Intragastric administration of berberine to mice produces hypoglycaemic effects with doses of 50–100 mg/kg (*27–29*).

Local injection of berberine into lesions caused by *Leishmania braziliensis panamensis* in hamsters reduced lesion size by approximately 50% (*30*).

Clinical pharmacology

Despite the large number of published clinical studies, only two have examined the effect of berberine in comparison with a positive control, such as tetracycline, on fluid loss caused by diarrhoea in patients with cholera or in non-cholera diarrhoea (*14*, *31–33*). In the first study, berberine chloride 100 mg was administered orally four times daily. The alkaloid did not have any significant vibriostatic effect; instead it only slightly reduced stool volume, and possibly reduced the vibriostatic effect of tetracycline (*32*). Berberine or tetracycline was no better than a placebo in patients with non-cholera diarrhoea of unspecified etiologies (*32*). A randomized controlled trial of 165 patients utilized a 400 mg single-bolus dose of berberine sulfate for enterotoxigenic *Escherichia coli*-induced diarrhoea and either 400 mg as a single oral dose or 1200 mg of berberine sulfate (400 mg every 8 hours) for the treatment of cholera (*33*). Berberine significantly reduced stool volume during enterotoxigenic *E. coli* (ETEC) diarrhoea regardless of strain and had a slight antisecretory activity in patients with cholera. No adverse effects were observed in the patients receiving berberine. The results of this study indicated that berberine was an effective and safe antisecretory drug for ETEC diarrhoea, but that it had only a modest antisecretory effect in cholera patients, where the activity of tetracycline alone was superior (*33*).

Berberine has been used therapeutically in the treatment of cutaneous leishmaniasis ("oriental sore") by direct injection of the drug into local lesions.

In humans, injection of a preparation containing 2% berberine into lesions caused by *Leishmania tropica* was an effective treatment (*34–36*).

Contraindications

The safety of berberine or extracts of Rhizoma Coptidis in pregnancy has not been established (*14*). Therefore, until such data are available the use of berberine during pregnancy is contraindicated.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

The safety of berberine or extracts of Rhizoma Coptidis has not been established with respect to fertility (*14*). There are conflicting reports as to the mutagenicity of Rhizoma Coptidis and berberine (*37–43*).

Pregnancy: non-teratogenic effects

The safety of berberine or extracts of Rhizoma Coptidis has not been established with respect to pregnancy. See Contraindications, above.

Nursing mothers

Excretion of berberine or Rhizoma Coptidis into breast milk, and its effects on the newborn have not been established; therefore, use of the herb during lactation is not recommended.

Paediatric use

The safety and efficacy of Rhizoma Coptidis or berberine in children have not been established.

Other precautions

No information available concerning general precautions, drug interactions, drug and laboratory test interactions, or teratogenic effects on pregnancy.

Adverse reactions

Berberine was reported to be well tolerated in therapeutic doses of 500 mg, and no serious intoxication was reported in humans (*44*). One report of nausea, vomiting, enterocinetic sound, abdominal distortion, diarrhoea, polyuria, and

erythropenia after administration of oral Rhizoma Coptidis to human adults (*45*) does not state the dosage used. No systematic studies have assessed organ function during acute or chronic administration of berberine salts or extracts of Rhizoma Coptidis (*14*).

Posology

Maximum daily oral dosage of crude plant material: 1.5–6 g (*1*, *3*).

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Rhizoma Curcumae Longae

Definition

Rhizoma Curcumae Longae is the dried rhizome of *Curcuma longa* L. (Zingiberaceae) (*1*).

Dried rhizomes of *Curcuma wenyujin* Y.H. Lee et C. Ling, *C. kwangsiensis* S. Lee et C.F. Liang. and *C. phaeocaulis* Val. are also official sources of Radix Curcumae or Turmeric Root-Tuber in China (*2*).

Synonyms

Curcuma domestica Valeton., *C. rotunda* L., *C. xanthorrhiza* Naves, *Amomum curcuma* Jacq. (*3–5*).

Selected vernacular names

Acafrao, arqussofar, asabi-e-safr, avea, cago rerega, chiang-huang, common tumeric, curcum, curcuma, dilau, dilaw, Gelbwurzel, gezo, goeratji, haladi, haldi, haldu, haku halu, hardi, haridra, huang chiang, hsanwen, hurid, Indian saffron, jiânghuang, kaha, kakoenji, kalo haledo, khamin chan, khaminchan, kilunga kuku, kitambwe, kiko eea, koening, koenit, koenjet, kondin, kooneit, kunyit, kurcum, kurkum, Kurkumawurzelstock, luyang dilaw, mandano, manjano, manjal, nghe, nisha, oendre, pasupu, rajani, rame, renga, rhizome de curcuma, saffran vert, safran, safran des indes, skyer-rtsa, tumeric, tumeric root, tumeric rhizome, turmeric, ukon, ul gum, wong keong, wong keung, yellow root, yii-chin, zardchob (*1–3*, *6–14*).

Description

Perennial herb up to 1.0 m in height; stout, fleshy, main rhizome nearly ovoid (about 3 cm in diameter and 4 cm long). Lateral rhizome, slightly bent (1 cm × 2–6 cm), flesh orange in colour; large leaves lanceolate, uniformly green, up to 50 cm long and 7–25 cm wide; apex acute and caudate with tapering base, petiole and sheath sparsely to densely pubescent. Spike, apical, cylindrical, 10–15 cm long and 5–7 cm in diameter. Bract white or white with light green upper half, 5–6 cm long, each subtending flowers, bracteoles up to 3.5 cm long. Pale yellow flowers about 5 cm long; calyx tubular, unilaterally split, unequally toothed; corolla white, tube funnel shaped, limb 3-lobed. Stamens lateral, petaloid, widely elliptical, longer than the anther; filament united to anther

about the middle of the pollen sac, spurred at base. Ovary trilocular; style glabrous. Capsule ellipsoid. Rhizomes orange within (*1*, *4*, *6*, *15*).

Plant material of interest: dried rhizome

General appearance

The primary rhizome is ovate, oblong or pear-shaped round turmeric, while the secondary rhizome is often short-branched long turmeric; the round form is about half as broad as long; the long form is from 2–5 cm long and 1–1.8 cm thick; externally yellowish to yellowish brown, with root scars and annulations, the latter from the scars of leaf bases; fracture horny; internally orange-yellow to orange; waxy, showing a cortex separated from a central cylinder by a distinct endodermis (*1*, *9*, *13*).

Organoleptic properties

Odour, aromatic; taste, warmly aromatic and bitter (*1*, *9*, *13*). Drug when chewed colours the saliva yellow (*9*).

Microscopic characteristics

The transverse section of the rhizome is characterized by the presence of mostly thin-walled rounded parenchyma cells, scattered vascular bundles, definite endodermis, a few layers of cork developed under the epidermis and scattered oleoresin cells with brownish contents. The cells of the ground tissue are also filled with many starch grains. Epidermis is thin walled, consisting of cubical cells of various dimensions. The cork cambium is developed from the subepidermal layers and even after the development of the cork, the epidermis is retained. Cork is generally composed of 4–6 layers of thin-walled brick-shaped parenchymatous cells. The parenchyma of the pith and cortex contains curcumin and is filled with starch grains. Cortical vascular bundles are scattered and are of collateral type. The vascular bundles in the pith region are mostly scattered and they form discontinuous rings just under the endodermis. The vessels have mainly spiral thickening and only a few have reticulate and annular structure (*1*, *8*, *9*).

Powdered plant material

Coloured deep yellow. Fragments of parenchymatous cells contain numerous altered, pasty masses of starch grains coloured yellow by curcumin, fragments of vessels; cork fragments of cells in sectional view; scattered unicellular trichomes; abundant starch grains; fragments of epidermal and cork cells in surface view; and scattered oil droplets, rarely seen (*1*, *13*).

Geographical distribution

Cambodia, China, India, Indonesia, Lao People's Democratic Republic, Madagascar, Malaysia, the Philippines, and Viet Nam (*1*, *13*, *16*). It is exten-

sively cultivated in China, India, Indonesia, Thailand and throughout the tropics, including tropical regions of Africa (*1*, *7*, *13*, *16*).

General identity tests

Macroscopic and microscopic examinations; test for the presence of curcuminoids by colorimetric and thin-layer chromatographic methods (*1*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Rhizoma Curcumae Longae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*17*–*19*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 2% (*1*, *9*).

Total ash

Not more than 8.0% (*1*, *15*).

Acid-insoluble ash

Not more than 1% (*1*, *9*, *15*).

Water-soluble extractive

Not less than 9.0% (*1*).

Alcohol-soluble extractive

Not less than 10% (*1*).

Moisture

Not more than 10% (*1*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Rhizoma Curcumae Longae is not more than 0.05 mg/kg (*19*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*17*) and guidelines for predicting dietary intake of pesticide residues (*20*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*17*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*17*).

Other purity tests

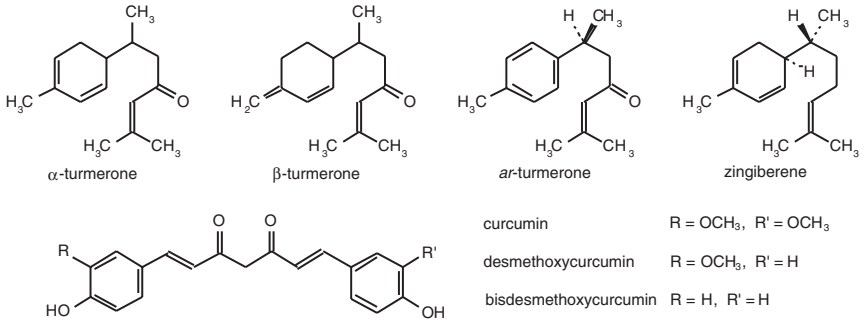
Chemical tests to be established in accordance with national requirements.

Chemical assays

Not less than 4.0% of volatile oil, and not less than 3.0% of curcuminoids (*1*). Qualitative analysis by thin-layer and high-performance liquid chromatography (*1*, *21*) and quantitative assay for total curcuminoids by spectrophotometric (*1*, *22*) or by high-performance liquid chromatographic methods (*23*, *24*).

Major chemical constituents

Pale yellow to orange-yellow volatile oil (6%) composed of a number of monoterpenes and sesquiterpenes, including zingiberene, curcumene, α- and β-turmerone among others. The colouring principles (5%) are curcuminoids, 50–60% of which are a mixture of curcumin, monodesmethoxycurcumin and bisdesmethoxycurcumin (*1*, *6*, *25*). Representative structures of curcuminoids are presented below.



Dosage forms

Powdered crude plant material, rhizomes (*1*, *2*), and corresponding preparations (*25*). Store in a dry environment protected from light. Air dry the crude drug every 2–3 months (*1*).

Medicinal uses

Uses supported by clinical data

The principal use of Rhizoma Curcumae Longae is for the treatment of acid, flatulent, or atonic dyspepsia (*26–28*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of peptic ulcers, and pain and inflammation due to rheumatoid arthritis (*2*, *11*, *14*, *29*, *30*) and of amenorrhoea, dysmenorrhoea, diarrhoea, epilepsy, pain, and skin diseases (*2*, *3*, *16*).

Uses described in folk medicine, not supported by experimental or clinical data

The treatment of asthma, boils, bruises, coughs, dizziness, epilepsy, haemorrhages, insect bites, jaundice, ringworm, urinary calculi, and slow lactation (*3*, *7*, *8–10*, *14*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

The anti-inflammatory activity of Rhizoma Curcumae Longae has been demonstrated in animal models (*3*, *30–32*). Intraperitoneal administration of the drug in rats effectively reduced both acute and chronic inflammation in carrageenin-induced paw oedema, the granuloma pouch test, and the cotton pellet granuloma test (*32*, *33*). The effectiveness of the drug in rats was reported to be similar to that of hydrocortisone acetate or indometacin in experimentally induced inflammation (*31*, *32*). Oral administration of turmeric juice or powder did not produce an anti-inflammatory effect; only intraperitoneal injection was effective (*33*). The volatile oil has exhibited anti-inflammatory activity in rats against adjuvant-induced arthritis, carrageenin-induced paw oedema, and hyaluronidase-induced inflammation (*32*). The anti-inflammatory activity appears to be mediated through the inhibition of the enzymes trypsin and hyaluronidase (*33*). Curcumin and its derivatives are the active anti-inflammatory constituents of the drug (*34–40*). After intraperitoneal administration, curcumin and sodium curcuminate exhibited strong anti-inflammatory activity in the carrageenin-induced oedema test in rats and mice (*41*). Curcumin was also found to be effective after oral administration in the acute carrageenin-induced oedema test in mice and rats (*41*). The anti-inflammatory activity of curcumin may be due to its ability to scavenge oxygen radicals, which have been implicated in the inflammation process (*42*). Furthermore, intraperitoneal injection of a polysaccharide fraction, isolated from the drug, increased phagocytosis capacity in mice in the clearance of colloidal carbon test (*43*).

Activity against peptic ulcer and dyspepsia

Oral administration to rabbits of water or methanol extracts of the drug significantly decreased gastric secretion (*44*) and increased the mucin contents of gastric juice (*45*). Intragastric administration of an ethanol extract of the drug to rats effectively inhibited gastric secretion and protected the gastroduodenal mucosa against injuries caused by pyloric ligation, hypothermic-restraint stress, indometacin, reserpine, and mercaptamine administration, and cytodestructive agents such as 80% methanol, 0.6 mol/l hydrochloric acid, 0.2 mol/l sodium hydroxide and 25% sodium chloride (*30*, *46*). The drug stimulated the production of gastric wall mucus, and it restored non-protein sulfides in rats (*46*, *47*). Curcumin, one of the anti-inflammatory constituents of the drug, has been shown to prevent and ameliorate experimentally induced gastric lesions in animal models by stimulation of mucin production (*48*). However, there are conflicting reports regarding the protective action of curcumin against histamine-induced gastric ulceration in guinea-pigs (*41*). Moreover, both intraperitoneal and oral administration of curcumin (100 mg/kg) have been reported to induce gastric ulceration in rats (*41*, *49–51*).

Non-specific inhibition of smooth muscle contractions in isolated guinea-pig ileum by sodium curcuminate has been reported (*41*).

The effect of curcumin on intestinal gas formation has been demonstrated *in vitro* and *in vivo*. Addition of curcumin to *Clostridium perfringens* of intestinal origin *in vitro* and to a chickpea flour diet fed to rats led to a gradual reduction in gas formation (*41*).

Both the essential oil and sodium curcuminate increase bile secretion after intravenous administration to dogs (*41*). In addition, gall-bladder muscles were stimulated (*39*).

Clinical pharmacology

Oral administration of the drug to 116 patients with acid dyspepsia, flatulent dyspepsia, or atonic dyspepsia in a randomized, double-blind study resulted in a statistically significant response in the patients receiving the drug (*27*). The patients received 500 mg of the powdered drug four times daily for 7 days (*27*). Two other clinical trials which measured the effect of the drug on peptic ulcers showed that oral administration of the drug promoted ulcer healing and decreased the abdominal pain involved (*28*, *29*).

Two clinical studies have shown that curcumin is an effective anti-inflammatory drug (*52*, *53*). A short-term (2 weeks) double-blind, crossover study of 18 patients with rheumatoid arthritis showed that patients receiving either curcumin (1200 mg/day) or phenylbutazone (30 mg/day) had significant improvement in morning stiffness, walking time and joint swelling (*52*). In the second study, the effectiveness of curcumin and phenylbutazone on postoperative inflammation was investigated in a double-blind study (*53*). Both drugs produced a better anti-inflammatory response than a placebo (*53*), but the

degree of inflammation in the patients varied greatly and was not evenly distributed among the three groups.

Contraindications

Obstruction of the biliary tract. In cases of gallstones, use only after consultation with a physician (*26*). Hypersensitivity to the drug.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Rhizoma Curcumae Longae is not mutagenic *in vitro* (*54–56*).

Pregnancy: teratogenic effects

Orally administered Rhizoma Curcumae Longae was not tetratogenic in mice or rats (*34*, *57*, *58*).

Pregnancy: non-teratogenic effects

The safety of Rhizoma Curcumae Longae during pregnancy has not been established. As a precautionary measure the drug should not be used during pregnancy except on medical advice (*59*).

Nursing mothers

Excretion of the drug into breast milk and its effects on the newborn have not been established. Until such data are available, the drug should not be used during lactation except on medical advice.

Paediatric use

The safety and effectiveness of the drug in children has not been established.

Other precautions

No information on drug interactions or drug and laboratory test interactions was found.

Adverse reactions

Allergic dermatitis has been reported (*60*). Reactions to patch testing occurred most commonly in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Persons who were not previously exposed to the drug had few allergic reactions (*60*).

Posology

Crude plant material, 3–9 g daily (*5*, *6*); powdered plant material, 1.5–3.0 g daily (*9*, *19*); oral infusion, 0.5–1 g three times per day; tincture (1 : 10) 0.5–1 ml three times per day.

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Radix Echinaceae

Definition

Radix Echinaceae consists of the fresh or dried roots of *Echinacea angustifolia* D.C. var. *angustifolia* or its variety *strigosa* McGregor, or *E. pallida* (Nutt.) Nutt. (Asteraceae) (*1–3*).

Synonyms

Echinacea angustifolia D.C. var. angustifolia

Brauneria angustifolia Heller, *Echinacea pallida* var. *angustifolia* (D.C.) Cronq. (*4, 5*).

Echinacea pallida (Nutt.) Nutt.

Echinacea angustifolia Hook, *Rudbeckia pallida* Nutt., *Brauneria pallida* Britt., *Echinacea pallida* f. *albida* Steyerm (*4, 5*).

E. angustifolia and *E. pallida* were regarded as varieties of the same species or even identical plants. However, in a revision of the genus *Echinacea* in 1968, McGregor (*4*) classified them as two distinct species with *E. angustifolia* further divided into two varieties (*4, 5*). A considerable amount of commercial "*E. angustifolia*" cultivated in Europe was, in fact, *E. pallida*. Data on *E. angustifolia* published prior to 1987 and based on material of commerce from Europe should be reviewed with caution (*5*).

Current commercial preparations are derived primarily from *E. angustifolia* and *E. pallida* roots; the preparation of a monograph on *E. purpurea* root awaits further data.

Asteraceae are also known as Compositae.

Selected vernacular names

Echinacea angustifolia D.C. var. angustifolia

American coneflower, black sampson, cock up head, coneflower, echinacea root, Igelkopf, Indian head, Kansas snakeroot, Kegelblume, narrow-leaved purple coneflower root, purple coneflower, Sonnenhut, racine d'echinacea (*5–10*).

Echinacea pallida (Nutt.) Nutt.

Blasser Igelkopf, blasse Kegelblume, blasser Sonnenhut, pale coneflower root, pale purple coneflower root, pallida root (*8, 10*).

Description

Echinacea species are hardy, herbaceous perennials with either simple or branched stems. The terminal single flowering heads have fertile disc florets that terminate in spines (paleae). These are surrounded by infertile drooping or spreading ray flowers that have 2 or 3 teeth at each end. The leaf shape varies from lanceolate to ovate, its margin may be dentate and the leaf may be pubescent or smooth. Roots are either single taproot or fibrous in form (*6–11*).

Echinacea angustifolia D.C. var. angustifolia

Stems simple or occasionally branched, 10–50 cm high, smooth or hirsute below, hirsute or tuberculate-hispid above; leaves oblong-lanceolate to elliptical, entire, dark green tuberculate-hirsute to tuberculate-hispid; basal leaves short- to long-petiolate, 5–27 cm long, 1–4 cm broad, lower cauline leaves petiolate, 4–15 cm long, 0.5–3.8 cm broad, upper cauline leaves sessile, acute; heads 1.5–3 cm high, 1.5–2.5 cm broad exclusive of ligules, phyllaries in three or four series, lanceolate, acute, entire, 6–11 mm long, 2–3 mm wide, tuberculate-hirsute or tuberculate-hispid; rays spreading, 2–3.8 cm long, 5–8 mm wide, white, pinkish or purplish; disc corollas 6–8.5 mm long, lobes 1.2–2 mm long; achenes 4–5 mm long, pappus a toothed crown; pollen grains yellow, 19–26 μm in diameter; haploid chromosome number $n = 11$ (*4*).

Echinacea pallida (Nutt.) Nutt.

Stems simple, rarely branched, 40–90 cm high, sparsely hirsute below, more densely so above; leaves oblong-lanceolate to long-elliptical, entire, dark green, hirsute on both surfaces, triple-veined; basal leaves 10–35 cm long, 1–4 cm broad, the cauline leaves 10–25 cm long, 1–2.5 cm broad, acute, petiolate below to sessile above; phyllaries lanceolate to narrowly oblong, 8–17 mm long, 2–4 mm broad, hirsute, ciliate, three or four series gradually passing into the echinaceous pales; rays reflexed, 4–9 cm long, 5–8 mm broad, purplish, pink, or white; pales 1–1.3 cm long, body 8–10 mm long, awn 2.5–3.5 mm long; disc floret 8–10 mm long, lobes 2–3 mm long, achenes 3.7–5 mm long, glabrous, pappus a toothed crown, teeth about even, longest 1 mm; pollen grains white, 24–28.5 μm in diameter; haploid chromosome number $n = 22$ (*4*).

Plant material of interest: fresh or dried roots

General appearance

Echinacea angustifolia D.C. var. *angustifolia*

Cylindrical or slightly tapering and sometimes spirally twisted, passing imperceptibly into a rhizome in the upper part; rhizome up to about 15 mm in diameter, roots 4–10 mm in diameter; outer surface pale brown to yellowish brown; rhizomes crowned with remains of the aerial stem and sometimes showing surface annulations; roots longitudinally wrinkled and deeply fur-

rowed; fracture short when dry but becoming tough and pliable on exposure to air (*12*).

***Echinacea pallida* (Nutt.) Nutt.**

Similar in appearance to *E. angustifolia* (*5–7*).

Organoleptic properties

Odour, mild, aromatic; taste, sweet initially but quickly becoming bitter followed by a tingling sensation on the tongue (*12*).

Microscopic characteristics

The roots of the two species are very similar. The transverse section shows a thin outer bark separated by a distinct cambium line from a wide xylem; a small circular pith in the rhizome. Cork composed of several rows of thin-walled cells containing yellowish brown pigment; cortex parenchymatous; rhizome with occasional small groups of thick-walled, lignified fibres in the pericycle; phloem and xylem composed of very narrow strands of vascular tissue separated by wide, non-lignified medullary rays; xylem vessels lignified, 25–75 μm in diameter, usually reticulate thickening but occasionally with spiral or annular thickening; stone cells, occurring singly or in small groups, varying considerably in size and shape from rounded to rectangular to elongated and fibre-like, up to 300 μm long and 20–40 μm wide, with intercellular spaces containing a dense black deposit; schizogenous oleoresin canals; spherocrystalline masses of inulin occur throughout the parenchymatous tissue. In *E. angustifolia* oleoresin canals, 80–150 μm in diameter and containing yellowish orange oleoresin, are present only outside the central cylinder, but in *E. pallida* they are present both inside and outside. In *E. angustifolia* the narrow, 300–800 μm long, lignified fibres are in scattered groups usually surrounded by phytomelanin deposits, while in *E. pallida* they are present only in the periphery of the cortex and they are mostly single, wider, and shorter, 100–300 μm, and phytomelanin is often absent (*9*, *12*).

Powdered plant material

E. angustifolia

Powdered rhizome and roots are brown with a slight aromatic odour and initially a sweet taste, quickly becoming bitter and leaving a tingling sensation on the tongue. Thin-walled polygonal cork cells with red-brown contents; lignified reticulately thickened vessels; abundant stone cells of various shapes; fragments of oleoresin canals with reddish brown contents; abundant thin-walled parenchyma with spherocrystalline masses of inulin (*12*).

E. pallida

Descriptions of powdered *E. pallida* are currently unavailable.

Geographical distribution

Echinacea species are native to the Atlantic drainage area of the United States of America and Canada, but not Mexico. Their distribution centres are in Arkansas, Kansas, Missouri, and Oklahoma in the United States of America (*4*). *E. pallida* was cultivated in Europe for a number of years and was mistaken for *E. angustifolia* (*9*).

General identity tests

Macroscopic and microscopic examinations (*5–7*, *9*, *12*). Chemical finger-prints of lipophilic constituents, echinacosides, and other caffeic acid derivatives in methanol extracts can be obtained by thin-layer chromatography and high-performance liquid chromatography (*5*, *13*, *14*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Echinaceae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*15–17*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 3% (*2*, *3*, *12*). Does not contain roots of *Parthenium integrifolium* L., commonly known as "American feverfew", which have been found to be adulterants of or substitutes for Radix Echinaceae (*5*, *6*, *9*, *13*).

Total ash

Not more than 9% (*12*).

Acid-insoluble ash

Not more than 3% (*12*).

Water-soluble extractive

Not less than 15% (*12*).

Moisture

Not more than 10% (*3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Radix Echinaceae is not more

than 0.05 mg/kg (*17*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residues (*18*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

Chemical tests and tests of dilute ethanol-soluble extractive to be established in accordance with national requirements.

Chemical assays

Essential oil (0.2–2%) and echinacoside (0.4–1.7%) in both *E. angustifolia* and *E. pallida* roots (*5*).

Quantitative analysis of echinacoside, cynarin, chicoric acid, chlorogenic acid derivatives, and other constituents by high-performance liquid chromatography (*5, 19*).

Major chemical constituents

A number of chemical entities have been identified and reported to be biologically active, including a volatile oil, alkamides, polyalkenes, polyalkynes, caffeic acid derivatives, and polysaccharides (*5–7, 9–11*).

The volatile oil contains, among other compounds, pentadeca-(1,8-*Z*)-diene (44%), 1-pentadecene, ketoalkynes and ketoalkenes.

More than 20 alkamides, mostly isobutylamides of C_{11}–C_{16} straight-chain fatty acids with olefinic or acetylenic bonds, or both, are found in the roots; the highest concentration is in *E. angustifolia*, followed by *E. purpurea*, and the lowest is in *E. pallida.* The main alkamide is a mixture of isomeric dodeca-2,4,8,10-tetraenoic acid isobutylamides.

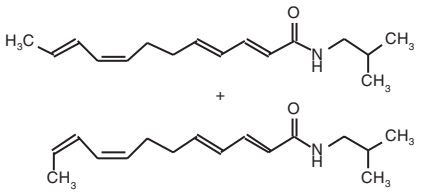
Caffeic acid ester derivatives present include echinacoside, cynarin, and chicoric acid. Cynarin is present only in *E. angustifolia*, thus distinguishing it from the closely related *E. pallida*.

Polysaccharide constituents are of two types: a heteroxylan of relative molecular mass about 35 000 and an arabinorhamnogalactan of relative molecular mass about 45 000.

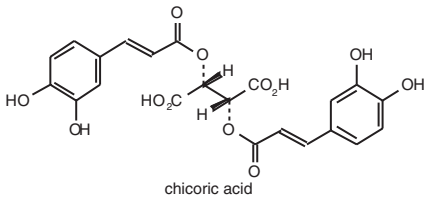
Other constituents include trace amounts of pyrrolizidine alkaloids (tussilagine (0.006%) and isotussilagine). At these concentrations, the alkaloids

are considered to be non-toxic (*7*, *20*), and since they lack the 1,2-unsaturated necine ring of alkaloids such as senecionine (structure in box) from *Senecio* species, they are considered to have no hepatotoxic potential (*5*).

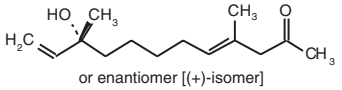
Structures of representative constituents are presented below.



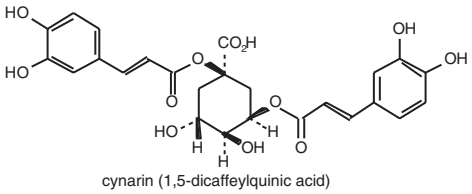
(2*E*,4*E*,8*Z*,10*E*)- and (2*E*,4*E*,8*Z*,10*Z*)-dodeca-2,4,8,10-tetraenoic acid isobutylamides



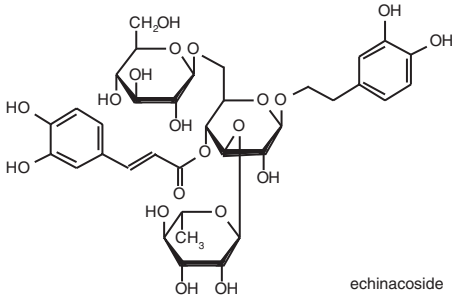
chicoric acid



or enantiomer [(+)-isomer] echinolone

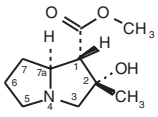


cynarin (1,5-dicaffeylquinic acid)

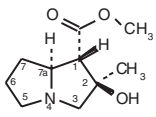


echinacoside

Necine ring pyrrolizidine alkaloids :

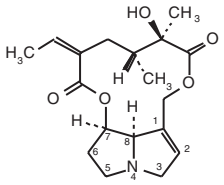


tussilagine



isotussilagine

1,2-saturated



senecionine

1,2-unsaturated

Dosage forms

Powdered roots, and galenics and preparations thereof for internal use (*9*).

Medicinal uses

Uses supported by clinical data

Preparations of Radix Echinaceae are administered orally in supportive therapy for colds and infections of the respiratory and urinary tract (*1*, *5–7*, *9*, *11*, *21–23*). Beneficial effects in the treatment of these infections are generally thought to be brought about by stimulation of the immune response (*5*, *6*, *9*, *10*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of yeast infections, side-effects of radiation therapy, rheumatoid arthritis, and food poisoning (*1*, *5*, *6*, *9*, *24*).

Pharmacology

Experimental pharmacology

Current claims for the effectiveness of Radix Echinaceae as a stimulator of the immune system are based on over 350 scientific studies in the past 50 years. Numerous *in vitro* and *in vivo* studies have documented the activation of an immune response after treatment with Radix Echinaceae extracts. The immunostimulant effect is brought about by three mechanisms: activation of phagocytosis and stimulation of fibroblasts; increasing respiratory activity; and causing increased mobility of the leukocytes (*5*, *9*, *11*). Chemically standardized extracts, derived from roots and aerial parts from the three *Echinacea* species, have been assessed for their phagocytotic potential. All ethanolic root extracts increased phagocytosis *in vitro* (*25*). Inhibition of hyaluronidase activity, stimulation of the activity of the adrenal cortex, stimulation of the production of properdin (a serum protein which can neutralize bacteria and viruses), and stimulation of interferon production have also been reported after *Echinacea* treatments (*26*). The pharmacological activity of *Echinacea* spp. has been attributed to five component fractions in addition to the essential oil, namely the alkylamides, caffeic acid derivatives, polyalkynes, polyalkenes and polysaccharides (*6*). The lipophilic amides, alkamides and caffeic acid derivatives appear to contribute to the immunostimulant activity of the alcoholic *Echinacea* extracts by stimulating phagocytosis of polymorphonuclear neutrophil granulocytes (*5*, *23*, *27*). High molecular weight polysaccharides, including heteroxylan, which activates phagocytosis, and arabinogalactan, which promotes the release of tumour necrosis factor and the production of interleukin-1 and interferon beta (*24*, *26*), have also been implicated in the activity of the aqueous extracts and the powdered drug when taken orally. The overall immunostimulant activity of

the alcoholic and aqueous *Echinacea* extracts appears to depend on the combined effects of several constituents (*5*, *9*, *27*).

Echinacea extracts inhibit streptococcal and tissue hyaluronidase (*28*). Inhibition of tissue and bacterial hyaluronidase is thought to localize the infection and prevent the spread of causative agents to other parts of the body. In addition to the direct antihyaluronidase activity, an indirect effect on the hyaluronic acid–hyaluronidase system has been reported (*29*, *30*). Stimulation of new tissue production by increasing the activity of fibroblasts, and stimulation of both blood- and tissue-produced phagocytosis, appear to be involved in this mechanism (*29*).

Echinacea extracts have anti-inflammatory activity. An alkylamide fraction from *Echinacea* roots markedly inhibited activity *in vitro* in the 5-lipoxygenase model (porcine leukocytes) (*31*). Topical application of a crude polysaccharide extract from *E. angustifolia* has been reported to reduce inflammation in the rat paw oedema model (*32*, *33*).

Clinical pharmacology

One placebo-controlled clinical study of 160 patients with infections of the upper respiratory tract has been performed (*34*). Significant improvement was observed after patients were treated with an aqueous-alcoholic tincture (1:5) at 90 drops/day (900 mg roots). The duration of the illness decreased from 13 to 9.8 days for bacterial infections, and from 12.9 to 9.1 days for viral infections (*34*).

Contraindications

External use

Allergy to plants in the Asteraceae.

Internal use

Should not be used in serious conditions such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection and autoimmune disorders. *Echinacea* preparations should not be administered to people with a known allergy to any plant of the Asteraceae (*1*). Parenteral administration is rarely indicated owing to potential adverse side-effects (see Adverse reactions).

Warnings

None.

Precautions

General

Internal use should not exceed a period of 8 successive weeks (*1*).

Carcinogenesis, mutagenesis, impairment of fertility

Mutagenicity and carcinogenicity tests were negative (*5*, *9*, *35*). Doses up to a polysaccharide concentration of 500 µg/ml caused no increase in sister chromatid exchange or structural chromosome aberrations (*35*).

Pregnancy: teratogenic effects

There are no reliable studies on this subject. Therefore, administration of Radix Echinaceae during pregnancy is not generally recommended (*1*).

Nursing mothers

There are no reliable studies on this subject. Therefore, nursing mothers should not take Radix Echinaceae without consulting a physician (*1*).

Paediatric use

Oral administration of *Echinacea* preparations is not recommended for children, except on the advice of a physician.

Other precautions

No information was available concerning drug interactions, drug and laboratory test interactions, and non-teratogenic effects on pregnancy.

Adverse reactions

External use

Allergic reactions.

Internal use

Allergic reactions, shivering, fever, and headache.

Posology

E. angustifolia root

Unless otherwise prescribed, hot water (about 150 ml) is poured over about 0.5 teaspoon (about 1 g) of powdered plant material, allowed to steep for 10 minutes, passed through a strainer, and taken orally three times a day between meals (*7*).

Liquid extract (1:5, 45% ethanol), 0.5–1 ml three times daily (*7*). Tincture (1:5, 45% ethanol), 2–5 ml three times daily (*7*).

E. pallida root

Unless otherwise prescribed: daily dose, tincture (1:5 with 50% ethanol by volume) from original dry extract (50% ethanol), corresponding to 900 mg of root (*9*).

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Herba Echinaceae Purpureae

Definition

Herba Echinaceae Purpureae consists of the fresh or dried aerial parts of *Echinacea purpurea* (L.) Moench harvested in full bloom (Asteraceae) (*1*).

Synonyms

Brauneria purpurea (L.) Britt., *Echinacea intermedia* Lindl., *E. purpurea* (L.) Moench f., *E. purpurea* (L.) Moench var. *arkansana* Steyerm., *E. speciosa* Paxt., *Rudbeckia purpurea* L., *R. hispida* Hoffm., *R. serotina* Sweet (*2, 3*).

Asteraceae are also known as Compositae.

Selected vernacular names

Coneflower, purple coneflower herb, purpurfarbener Igelkopf, purpurfarbene Kegelblume, purpurfarbener Sonnenhut, red sunflower, roter Sonnenhut (*4–8*).

Description

A hardy, herbaceous perennial. Stems erect, stout, branched, hirsute or glabrous, 60–180 cm high; basal leaves ovate to ovate-lanceolate, acute, coarsely or sharply serrate, petioles up to 25 cm long, blades to 20 cm long and 15 cm wide, blade abruptly narrowing to base, often cordate, decurrent on petiole, 3–5 veined; cauline leaves petiolate below, sessile above, 7–20 cm long, 1.5–8 cm broad, coarsely serrate to entire, rough to the touch on both surfaces; phyllaries linear-lanceolate, attenuate, entire, pubescent on outer surface, ciliate, passing into the chaff; heads 1.5–3 cm long and 5–10 mm broad, purplish; pales 9–13 mm long, awn half as long as body; disc corollas 4.5–5.5 mm long, lobes 1 mm long; achene 4–4.5 mm long, pappus a low crown of equal teeth; pollen grains yellow, 19–21 μm in diameter; haploid chromosome number $n = 11$ (*2*).

Plant material of interest: fresh or dried aerial parts

General appearance

The macroscopic characteristics of Herba Echinaceae Purpureae are as described above under Description. An abbreviated description is currently unavailable.

Organoleptic properties

Mild, aromatic odour; initially sweet taste that quickly becomes bitter.

Microscopic characteristics

A description of the microscopic characteristics of a cross-section of the aerial parts of the plant is currently unavailable.

Powdered plant material

A description of the powdered plant material is currently unavailable.

Geographical distribution

Echinacea purpurea is native to the Atlantic drainage area of the United States of America and Canada, but not Mexico. Its distribution centres are in Arkansas, Kansas, Missouri, and Oklahoma in the United States of America (*2*). *Echinacea purpurea* has been introduced as a cultivated medicinal plant in parts of north and eastern Africa and in Europe (*9*).

General identity tests

Macroscopic examination *(2)* and thin-layer chromatography and high-performance liquid chromatography (*4*, *10–13*) of the lipophilic constituents and chicoric acid in methanol extracts.

Purity tests

Microbiology

The test for *Salmonella* spp. in Herba Echinaceae Purpureae should be negative. The maximum acceptable limits of other microorganisms are as follows (*14–16*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; Escherichia *coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; Escherichia *coli*—0/g or ml. Preparations for external use: aerobic bacteria—not more than 10^2/g or ml; fungi—not more than 10^2/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^1/g or ml.

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Echinaceae Purpureae is not more than 0.05 mg/kg (*16*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*14*) and guidelines for predicting dietary intake of pesticide residues (*17*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material *(14)*.

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*14*).

Other purity tests

Chemical tests and tests for acid-insoluble ash, dilute ethanol-soluble extractive, foreign organic matter, moisture, total ash, and water-soluble extractive to be established in accordance with national requirements.

Chemical assays

For essential oil (0.08–0.32%); chicoric acid (1.2–3.1%) (*4*). Quantitative analysis of echinacoside, chicoric acid, isobutylamides, and other constituents by high-performance liquid chromatography (*4*). Quantitative analysis of alkamides and caffeic acid derivatives by thin-layer chromatography and high-performance liquid chromatography (*4, 12*).

Major chemical constituents

A number of chemical entities have been identified, including alkamides, polyalkenes, polyalkynes, caffeic acid derivatives, and polysaccharides (*3, 5–9*).

The volatile oil contains, among other compounds, borneol, bornyl acetate, pentadeca-8-(*Z*)-en-2-one, germacrene D, caryophyllene, and caryophyllene epoxide.

Isobutylamides of C_{11}–C_{16} straight-chain fatty acids with olefinic or acetylenic bonds (or both) are found in the aerial parts of Herba Echinaceae Purpureae, with the isomeric dodeca-(2*E*,4*E*,8*Z*,10*E*/*Z*)-tetraenoic acid isobutylamides.

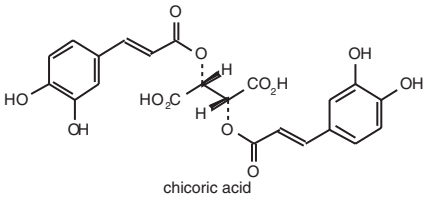
The caffeic acid ester derivative chicoric acid is the major active compound of this class found in the aerial parts of *Echinacea purpurea*, with a concentration range of 1.2–3.1%. Chicoric acid methyl ester and other derivatives are also present.

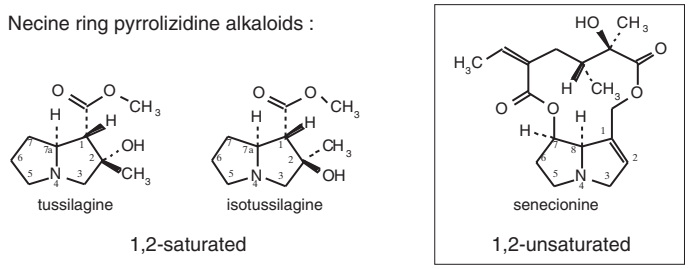
Polysaccharide constituents from Herba Echinaceae Purpureae are of two types: a heteroxylan of average relative molecular mass about 35 000 (e.g. PS-I), and an arabinorhamnogalactan of average relative molecular mass about 45 000 (e.g. PS-II).

Other constituents include trace amounts of pyrrolizidine alkaloids (tussilagine (0.006%) and isotussilagine). At these concentrations, the alkaloids

are considered to be non-toxic (*8*). Furthermore, because these alkaloids lack the 1,2-unsaturated necine ring of alkaloids such as senecionine (structure in box) from *Senecio* species, they are considered to be non-hepatotoxic (*3*).

Structures of representative constituents are presented below.





Dosage forms

Powdered aerial part, pressed juice and galenic preparations thereof for internal and external use *(1, 3)*.

Medicinal uses

Uses supported by clinical data

Herba Echinaceae Purpureae is administered orally in supportive therapy for colds and infections of the respiratory and urinary tract (*1, 3, 5, 7, 8, 18*). Beneficial effects in the treatment of these infections are generally thought to be brought about by stimulation of the immune response (*3, 5, 7*). External uses include promotion of wound healing and treatment of inflammatory skin conditions (*1, 3, 5, 7, 8, 9, 19*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

Other medical uses claimed for Herba Echinaceae Purpureae include treatment of yeast infections, side-effects of radiation therapy, rheumatoid arthritis, blood poisoning, and food poisoning (*1*, *5*, *7*, *9*).

Pharmacology

Experimental pharmacology

Current claims of the effectiveness of *Echinacea purpurea* as a stimulator of the immune system are based on numerous scientific studies. The immunostimulant effect is brought about by three mechanisms: activation of phagocytosis and stimulation of fibroblasts; increasing respiratory activity; and increased mobility of the leukocytes (*3*, *5*, *8*). Phagocytic activity of standardized extracts of the aerial parts of *E. purpurea* has been determined. A lyophylisate of the expressed juice of Herba Echinaceae Purpureae significantly increased the percentage of phagocytizing human granulocytes and stimulated the phagocytosis of yeast particles *in vitro* (*20*, *21*). Inhibition of hyaluronidase activity, stimulation of the activity of the adrenal cortex, stimulation of the production of properdin (a serum protein which can neutralize bacteria and viruses), and stimulation of interferon production have also been reported after *Echinacea* treatments (*22*). The pharmacological activity of *Echinacea* spp. has been attributed to five component fractions in addition to the essential oil, namely the alkylamides, caffeic acid derivatives, polyalkynes, polyalkenes, and polysaccharides (*7*). The lipophilic amides, alkamides, and caffeic acid derivatives appear to contribute to the immunostimulant activity of the alcoholic *Echinacea* extracts by stimulating phagocytosis of polymorphonuclear neutrophil granulocytes (*3*, *23*, *24*). High molecular weight polysaccharides, including heteroxylan, which activates phagocytosis, and arabinogalactan, which promotes the release of tumour necrosis factor and the production of interleukin-1 and interferon beta (*19*, *22*), have also been implicated in the activity of the aqueous extracts and the powdered drug when taken orally. The overall immunostimulant activity of the alcoholic and aqueous *Echinacea* extracts appears to depend on the combined effects of several constituents (*3*, *5*, *23*).

Topical applications of *Echinacea* extracts have been traditionally used to promote wound healing. The first published work on the mechanism of this action was by Büsing (*25*), who investigated the effect of *Echinacea* spp. on streptococcal and tissue hyaluronidase. Inhibition of tissue and bacterial hyaluronidase is thought to localize the infection and prevent the spread of causative agents to other parts of the body. In addition to the direct antihyaluronidase activity, an indirect effect on the hyaluronic acid–hyaluronidase system has been reported (*26*). Stimulation of new tissue production by increasing fibroblast activity, and stimulation of both blood- and tissue-produced phagocytosis, appear to be involved in this mechanism (*26*). The polysaccharide

fraction (echinacin B) appears to promote wound healing by forming a hyaluronic acid–polysaccharide complex that indirectly leads to the inhibition of hyaluronidase (*27*).

In *in vitro* experiments, an ethanol extract (65% by volume) of Herba Echinaceae Purpureae inhibited the contraction of collagen by mouse fibroblasts, measured by the collagen lattice diameter (*28*).

Mouse macrophages pretreated with polysaccharides that were isolated from the supernatant of Herba Echinaceae Purpureae cell culture increased production of tumour necrosis factor alpha, interleukin-1, and interferon beta-2 and increased cytotoxicity against tumour cells and microorganisms (*Leishmania enreittii*) (*29–31*).

Purified polysaccharides isolated from large-scale cell cultures of *E. purpurea* enhanced the spontaneous motility of human polymorphonuclear leukocytes under soft agar and increased the ability of these cells to kill *Staphylococcus aureus*. Human monocytes were activated to secrete tumour necrosis factor alpha, interleukin-1, and interleukin-6 while the expression of class II human leukocyte antigens was unaffected (*32*).

For purified caffeic acid derivatives, antiviral activities have been demonstrated (*33*). Incubation of vesicular stomatitis virus (VSV) with 125 μg/ml of chicoric acid for 4 hours reduced the number of viral particles in mouse L-929 murine cells by more than 50% (*34*).

Clinical pharmacology

Recently 26 controlled clinical trials (18 randomized, 11 double-blind) were systematically reviewed in Germany (*24*), Nineteen trials studied the prophylaxis or curative treatment of infections, four trials studied the reduction of side-effects of chemotherapy, and three investigated the modulation of specific immune parameters. The review concluded that *Echinacea*-containing preparations are efficacious immunomodulators (*24*). However, it also concluded that there was insufficient evidence for clear therapeutic recommendations as to which preparation or dosage to use for a specific indication (*24*).

A large-scale longitudinal trial (4598 patients) studied the effects of an ointment containing a lyophylisate of the expressed juice of Herba Echinaceae Purpureae. The ointment was used to treat inflammatory skin conditions, wounds, eczema, burns, herpes simplex, and varicose ulcerations of the legs (*19*). Therapeutic benefit from the ointment was observed in 85.5% of the cases. The treatment periods ranged from 7.1 to 15.5 days (*19*).

Contraindications

External use

Allergy to the plant.

Internal use

Should not be used in serious conditions such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection, and autoimmune disorders.

Echinacea preparations should not be administered to people with a known allergy to any plant of the Asteraceae (*1*).

Warnings

No information available.

Precautions

General

Internal or external use should not exceed a period of 8 successive weeks (*1*).

Carcinogenesis, mutagenesis, impairment of fertility

Mutagenicity and carcinogenicity test results were negative (*3*, *5*, *35*). Doses up to a polysaccharide concentration of 500 mg/ml caused no increase in sister chromatid exchange or structural chromosome aberrations (*35*).

Pregnancy: teratogenic effects

There are no reliable studies on this subject. Therefore, administration of the drug during pregnancy is not recommended (*1*).

Nursing mothers

There are no reliable studies on this subject. Nursing mothers should not take the drug without consulting a physician (*1*).

Paediatric use

Oral administration of *Echinacea* preparations is not recommended for small children, except on the advice of a physician. Herba Echinaceae Purpureae may be used for external treatment of small superficial wounds.

Other precautions

No information available concerning drug interactions, drug and laboratory test interactions, or non-teratogenic effects on pregnancy.

Adverse reactions

Occasionally allergic reactions may occur owing to allergy to plants in the Asteraceae (Compositae).

Posology

Oral daily dosage of Herba Echinaceae Purpureae, 6–9 ml expressed juice (*1*) for no longer than 8 successive weeks (*1*). External use of semisolid preparations containing at least 15% pressed juice (*1*) for no longer than 8 successive weeks (*1*). Information on dosages for children is not available (*7*).

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Herba Ephedrae

Definition

Herba Ephedrae consists of the dried stem or aerial part of *Ephedra sinica* Stapf or other ephedrine-containing *Ephedra* species (Ephedraceae) (*1–5*).

Synonyms

None.

Selected vernacular names

Amsania, budshur, chewa, Chinese ephedra, ephédra, horsetail, hum, huma, joint fir, khama, ma hoàng, ma huang, máhuáng, mao, maoh, maou, mao-kon, môc tac ma hoàng, mu-tsei-ma-huang, phok, san-ma-huang, shrubby, soma, song tuê ma hoàng, trung aa hoàng, tsao-ma-huang, tutgantha (*4–10*).

Description

Erect or prostrate, green, almost leafless shrub, 20–90 cm high. Branches erect, short, glaucous green, somewhat flat, 1.0–1.5 mm in diameter, with small sparse longitudinal striae, fasciated at the nodes; nodes reddish brown; internode 2.5–5.5 cm long × 2 mm in diameter. Small triangular leaves opposite, reduced to scales, barely 2 mm. Flowers in summer, unisexual, dioecious; male flowers pedunculate or nearly sessile, grouped in catkins composed of 4 to 8 pairs of flowers with about 8 anthers; female flowers biflorous, pedunculate with 3 or 4 pairs of bracts, the naked ovule surrounded by an urn-shaped perianth sheath, fruiting with often fleshy red succulent bracts, 2-seeded (*4*, *7*, *11*).

Plant material of interest: stem or aerial part

General appearance

Macroscopically, Herba Ephedrae occurs as thin cylindrical or ellipsoidal cylinder, 1–2 mm in diameter; 3.5–5.5 cm in length of internode; light green to yellow-green; numerous parallel vertical furrows on the surface; scaly leaves at the node portion; leaves, 2–4 mm in length, light brown to brown in colour, usually opposite at every node, adhering at the base to form a tubular sheath around the stem. Under a magnifying glass, the transverse section of the stem appears as circle and ellipse, the outer portion greyish green to yellow-green in

colour, and the centre filled with a red-purple substance or hollow. When fractured at an internode, the outer part is fibrous and easily split vertically (*1*).

Organoleptic properties

Odour, slight; taste, slightly bitter and astringent, giving a slight sensation of numbness on the tongue (*1*).

Microscopic characteristics

The epidermal cells of the stem are covered with a moderately thick granular cuticle; the cells are polygonal or subrectangular, axially elongated, having straight anticlinal walls. The stomata are few and are of the ranunculaceous type with lignified appendages. The epidermis of the scaly leaf is covered with smooth (upper) or warty (lower) cuticle and consists of subrectangular to polygonal cells, having straight or sometimes slightly beaded anticlinal walls; few stomata are present resembling those of stem. The epidermis of the apical and marginal regions of the scaly leaf shows short papillae-like outgrowths. Chlorenchymatous palisade-like cells form the outer zone of the cortex; rounded ordinary parenchymatous cells form the inner zone of the cortex. Cortical parenchyma and pith cells contain an amorphous reddish brown substance. Non-lignified or lignified hypodermal and pericyclic fibres, which have thick walls, bear slit-like pits and blunt, slightly tapering, occasionally forked ends. The vessels of the secondary xylem of the stem are lignified with bordered pits, having rounded or oval apertures. The vessel segments have much inclined end walls, bearing foraminate perforation plates. The tracheids and fibrous tracheids of secondary xylem of the stem are lignified with bordered pits having oval or slit-like apertures. The fibres of the scaly leaf are lignified, usually irregular or nearly straight, having moderately thick walls and blunt or sometimes forked ends. Few, small, rounded, simple and compound starch granules with indistinct hilum are present in cortical parenchyma, pith, and medullary ray cells. Few, small prisms of calcium oxalate are present in the cortical parenchyma (*4*).

Powdered plant material

Powdered Herba Ephedrae is greyish green. Numerous thick fragments of cutinized outer walls of epidermis vary from colourless to varying shades of brown or red; numerous fragments of sclerenchyma fibres with extremely thickened, non-lignified to lignified walls, narrow, frequently indistinct lumina and sharp pointed ends; fragments of vascular tissue showing tracheids with bordered pores and occasional spiral and pitted tracheae; numerous chlorenchyma cells; starch grains simple, spheroidal to occasionally ovate, averaging up to 1.2 μm but occasionally up to 20 μm; fragments of epidermis with rectangular cells and granular contents, some with sunken elliptical stomata; fragments of

lignified or non-lignified pith parenchyma, some of the cells showing mucilage sacs; papillae; granules of calcium oxalate (*4*, *6*).

Geographical distribution

Ephedra species are found in Afghanistan, Central America, China, India, regions of the Mediterranean, Mongolia, and North America (*4*, *6–12*).

General identity tests

Macroscopic and microscopic examinations and microchemical tests for the presence of alkaloids with Mayer's reagent (*1–5*, *7*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Herba Ephedrae products should be negative. The maximum acceptable limits for other microorganisms are as follows (*13–15*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Woody stems, not more than 5% (*1*). Does not contain stems of Equisetaceae or Gramineae plants, nor any other foreign matter (*1*).

Total ash

Not more than 9% (*3*).

Acid-insoluble ash

Not more than 2% (*1*).

Moisture

Not more than 9% (*3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Herba Ephedrae is not more than 0.05 mg/kg (*15*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*13*) and guidelines for predicting dietary intake of pesticide residues (*16*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*13*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*13*).

Other purity tests

Chemical, dilute ethanol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

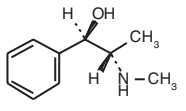
Chemical assays

Contains not less than 0.7% total alkaloids, calculated as ephedrine by high-performance liquid chromatography in the Japanese pharmacopoeia; or not less than 0.8% of total alkaloids, calculated as ephedrine in the Chinese pharmacopoeia (*1*, *2*).

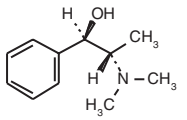
Thin-layer (*17*), gas–liquid (*18*) or high-performance liquid (*19*) chromatographic analysis for ephedrine and related alkaloids are available.

Major chemical constituents

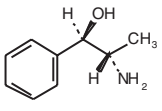
The major active principle found in Herba Ephedrae is (−)-ephedrine in concentrations of 40–90% of the total alkaloid fraction, accompanied by (+)-pseudoephedrine. Other trace alkaloids in the alkaloid complex include (−)-norephedrine, (+)-norpseudoephedrine, (−)-methylephedrine and (+)-methylpseudoephedrine. The total alkaloid content can exceed 2% depending on the species (*20*). Not all *Ephedra* species contain ephedrine or alkaloids.



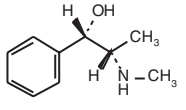
(−)-ephedrine



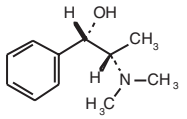
(−)-methylephedrine



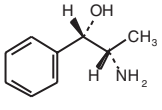
(−)-norephedrine



(+)-pseudoephedrine



(+)-methylpseudoephedrine



(+)-norpseudoephedrine

Dosage forms

Powdered plant material; extracts and other galenicals. Store in well closed, light-resistant containers.

Medicinal uses

Uses supported by clinical data

Herba Ephedrae preparations are used in the treatment of nasal congestion due to hay fever, allergic rhinitis, acute coryza, common cold, and sinusitis. The drug is further used as a bronchodilator in the treatment of bronchial asthma (*4*, *8*, *10*, *21–23*).

Uses described in pharmacopoeias and in traditional systems of medicine

Herba Ephedrae has been used for the treatment of urticaria, enuresis, narcolepsy, myasthenia gravis, and chronic postural hypotension (*4*, *8*, *22*, *23*).

Uses described in folk medicine, not supported by experimental or clinical data

Other medical uses claimed for Herba Ephedrae preparations include its use as an analgesic, an antiviral agent, an antitussive and expectorant, an antibacterial, and an immune stimulant (*10*, *24*, *25*).

Clinical pharmacology

Two of the main active constituents of Herba Ephedrae, ephedrine and pseudoephedrine, are potent sympathomimetic drugs that stimulate α-, β_1- and β_2- adrenoceptors (*22*, *23*). Pseudoephedrine's activity is similar to ephedrine, but its hypertensive effects and stimulation of the central nervous system are somewhat weaker. Part of ephedrine's peripheral action is due to the release of norepinephrine, but the drug also directly affects receptors. Tachyphylaxis develops to its peripheral actions, and rapidly repeated doses become less effective owing to the depletion of norepinephrine stores (*22*).

Cardiovascular actions

Like epinephrine (adrenaline), ephedrine excites the sympathetic nervous system, causing vasoconstriction and cardiac stimulation. Ephedrine differs from epinephrine in that it is orally active, has a much longer duration of action, and has more pronounced activity in the central nervous system, but is much less potent (*22*, *23*). The drug stimulates the heart rate, as well as cardiac output, and increases peripheral resistance, thereby producing a lasting rise in blood pressure. The cardiovascular effects of ephedrine persist up to ten times as long as

those of epinephrine (*22*). Ephedrine elevates both the systolic and diastolic pressures and pulse pressure. Renal and splanchnic blood flows are decreased, while coronary, cerebral, and muscle blood flows are increased (*22*, *23*).

Bronchodilator and nasal decongestant

Ephedrine, like epinephrine, relaxes bronchial muscles and is a potent bronchodilator owing to its activation of the β-adrenoceptors in the lungs (*22*, *23*). Bronchial muscle relaxation is less pronounced but more sustained with ephedrine than with epinephrine. As a consequence, ephedrine should be used only in patients with mild cases of acute asthma and in chronic cases that require maintenance medication. Ephedrine, like other sympathomimetics with α-receptor activity, causes vasoconstriction and blanching when applied topically to nasal and pharyngeal mucosal surfaces (*22*, *23*). Continued, prolonged use of these preparations (>3 days) may cause rebound congestion and chronic rhinitis (*26*). Both ephedrine and pseudoephedrine are useful orally as nasal decongestants in cases of allergic rhinitis, but they may not be very effective for the treatment of nasal congestion due to colds.

Central nervous system

Mydriasis occurs after local application of ephedrine (3–5%) to the eye, but the effect lasts for only a few hours (*22*). Ephedrine is of little value as a mydriatic in the presence of inflammation. The activity of the smooth muscles of the uterus is usually reduced by ephedrine; consequently, the drug has been used to relieve the pain of dysmenorrhoea (*22*).

Ephedrine is a potent stimulator of the central nervous system. The effects of the drug may last for several hours after oral administration (*23*). Thus, preparations containing Herba Ephedrae have been promoted for use in weight reduction and thermogenesis (fat burning) (*27*, *28*). The safety and effectiveness of these preparations is currently an issue of debate and requires further investigation (*29*).

Ephedrine stimulates the α-adrenoceptors of the smooth muscle cells of the bladder base, which increases the resistance to the outflow of urine (*23*). Thus Herba Ephedrae has been used in the treatment of urinary incontinence and nocturnal enuresis.

Contraindications

Herba Ephedrae should not be administered to patients with coronary thrombosis, diabetes, glaucoma, heart disease, hypertension, thyroid disease, impaired circulation of the cerebrum, phaeochromocytoma, or enlarged prostate (*10*, *21*, *23*). Co-administration of Herba Ephedrae preparations with monoamine oxidase inhibitors is contraindicated as the combination may cause severe, possibly fatal, hypertension (*23*).

Warnings

Dosage should be reduced or treatment discontinued if nervousness, tremor, sleeplessness, loss of appetite or nausea occurs. Not for children under 6 years of age. Keep out of the reach of children (*30*). Continued, prolonged use may cause dependency.

Precautions

General

Insomnia may occur with continued use of Herba Ephedrae preparations (*23*).

Drug interactions

In combination with cardiac glycosides or halothane, may cause heart rhythm disturbances (*21*); with guanethidine, may cause an enhancement of sympathomimetic effect (*21*); with monoamine oxidase inhibitors, can cause severe, possibly fatal, hypertension (*26*); with ergot alkaloid derivatives or oxytocin, may increase risk of high blood pressure (*21*).

Carcinogenesis, mutagenesis, impairment of fertility

Extracts of *Ephedra sinica* are not mutagenic in the *Salmonella*/microsome reversion assay (*31*).

Pregnancy: teratogenic effects

Ephedra sinica did not have any teratogenic effects *in vivo* (*32*).

Pregnancy: nonteratogenic effects

Ephedra sinica is not abortifacient in rats (*32*). Clinical studies in humans are not available; therefore, use of the drug during pregnancy is not generally recommended.

Nursing mothers

There are no reliable studies on this subject. Therefore, nursing mothers should not take Herba Ephedrae without consulting a physician.

Paediatric use

Herba Ephedrae should not be administered to children under 6 years of age.

Other precautions

No information available concerning drug and laboratory test interactions.

Adverse reactions

In large doses Herba Ephedrae products can cause nervousness, headaches, insomnia, dizziness, palpitations, skin flushing and tingling, and vomiting (*21*).

The principal adverse effects of ephedrine and Herba Ephedrae are stimulation of the central nervous system, nausea, tremors, tachycardia, and urine retention (*24*). Continued, prolonged use (>3 days) of topical preparations containing Herba Ephedrae, for the treatment of nasal congestion, may cause rebound congestion and chronic rhinitis (*26*). Continued prolonged use of oral preparations may cause dependency (*21*).

Posology

Crude plant material: 1–6 g for decoction daily (*8, 21*). Liquid extract (1 : 1 in 45% alcohol): 1–3 ml daily (*21*). Tincture (1 : 4 in 45% alcohol): 6–8 ml daily (*21*).

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Folium Ginkgo

Definition

Folium Ginkgo consists of the dried whole leaf of *Ginkgo biloba* L. (Ginkgoaceae).

Synonyms

Pterophyllus salisburiensis Nelson, *Salisburia adiantifolia* Smith, *Salisburia macrophylla* C. Koch (*1–4*).

Selected vernacular names

Eun-haeng, gin-nan, ginkgo, ginkgo balm, ginkgo leaves, ginkyo, ginan, icho, ityo, kew tree, maidenhair tree, pei-wen, temple balm, yin guo, yinhsing (*1–5*).

Description

A monotypic dioecious plant that is the only living representative of the Ginkgoales. It has a grey bark, reaches a height of 35 m and a diameter of 3–4 m (sometimes up to 7 m), and has fan-like leaves that are deciduous, alternate, lengthily petiolate, bilobate, base wedge-shaped, 6–9 cm broad (sometimes up to 15–20 cm), turning yellow in autumn. Venation dichotomously branching, seemingly parallel. Staminate and ovulate strobili borne on separate trees; staminate strobili consisting of naked pairs of anthers in catkin-like clusters; ovulate strobili in the form of long, slender, fused stalks bearing a single naked ovule which is fertilized by motile sperm cells, developing into 2 seeds. Seeds yellow when mature, foul-smelling, drupe-like, the middle layer of integument becoming hard or stone-like, the outer layer fleshy (*3*, *4*).

Plant material of interest: dried leaf

The kernel (nut, seed) is used in Chinese medicine (*6*, *7*).

General appearance

The leaves are green, grey-yellow, brown or blackish; the upper side of a leaf may be somewhat darker than the underside. The leaves are fan-shaped, long-petioled and have two lobes with forked veins radiating from the petiole end (*2*, *4*, *8*).

Organoleptic properties

Ginkgo leaves have a weak characteristic odour (*2*, *4*, *8*).

Microscopic characteristics

Young leaves have abundant trichomes that become confined to the petiole base as the leaf ages. While the leaves have no midrib, dichotomous venation with regular, numerous branching parallel veins arises from two vascular strands within the petiole. Stomata occur almost exclusively on the lower surface of the leaf. The epidermis of the upper and underside of the leaf consists of undulated, irregular, mostly long extended cells. In the cross-section, the epidermal cells appear nearly isodiametric and from above appear to be slightly undulated, with the upper cells appearing larger. The outer walls of the epidermal cells are covered with a more or less thin layer of cuticle. In the area of vascular bundles there are remarkable long extended narrow cells with slightly undulated walls. Numerous druses of calcium oxalate occur near the vascular bundles (*2*, *4*).

Powdered plant material

The colour of the powder agrees with that of the leaves. The powder shows fragments of the epidermis with wavelike indentations irregular in form with generally elongated cells; large stomal openings of the anisocytic type; markedly elongated, narrow cells with only weakly undulated walls in the vascular areas and without marked indentations. The equifacial mesophyll comprises excretory vesicles, secretory cells, and idioblasts, as well as intermittent calcium oxalate druses, in the region of the vascular fascicles (*2*, *8*).

Geographical distribution

Native to China, but grown as an ornamental shade tree in Australia, south-east Asia, Europe, Japan, and the United States of America (*1–3*, *6*). It is commercially cultivated in France and the United States of America (*2*).

General identity tests

Macroscopic and microscopic examinations (*2*, *8*). Thin-layer chromatographic analysis for the presence of the characteristic flavonoids, ginkgolides, and bilobalide (*9*); high-performance liquid chromatographic analysis for flavonoids (*10*), ginkgolides, and bilobalide (*2*); and gas–liquid chromatographic evaluation of ginkgolides and bilobalide (*11*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Folium Ginkgo should be negative. The maximum acceptable limits of other microorganisms are as follows (*12–14*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not

more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 5% of twigs and not more than 2% of other foreign matter (*15*).

Total ash

Not more than 11% (*15*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Folium Ginkgo is not more than 0.05 mg/kg (*14*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*12*), and guidelines for predicting dietary intake of pesticide residues (*16*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*12*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*12*).

Other purity tests

Acid-insoluble ash, acid-insoluble extractive, chemical, and moisture tests to be established in accordance with national requirements.

Chemical assays

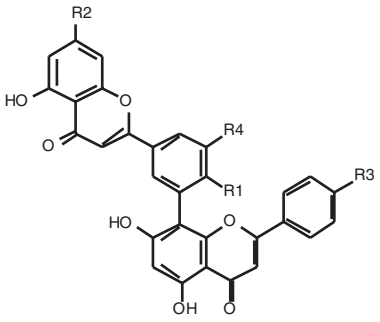
Flavonoids not less than 0.5% calculated as flavonol glycosides or 0.2–0.4% calculated as aglycones (*17*); also contains ginkgolides (0.06–0.23%) and bilobalide (up to 0.26%) (*2*, *17*).

Qualitative and quantitative determination of flavonoid glycosides is carried out after hydrolysis to the aglycones kaempferol, quercetin, and isorhamnetin. The qualitative presence or absence of biflavones (*17*) is determined by high-performance liquid chromatography; and qualitative and quantitative determination of the diterpene ginkgolides and sesquiterpene bilobalide by high-performance liquid chromatography (*2*, *18*) or gas–liquid chromatography (*11*).

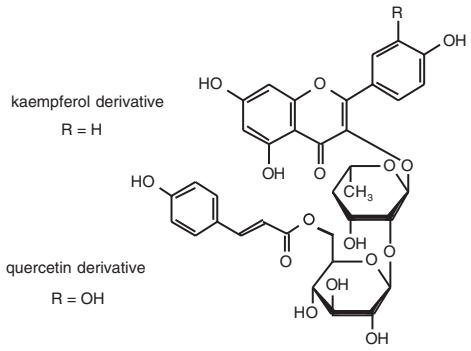
Certain commercial products used for clinical and experimental biological studies, e.g. EGb 761 and LI 1370, do not contain biflavones.

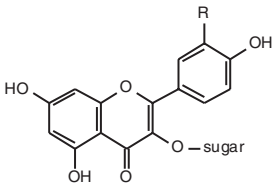
Major chemical constituents

Folium Ginkgo contains a wide variety of phytochemicals, including alkanes, lipids, sterols, benzenoids, carotenoids, phenylpropanoids, carbohydrates, flavonoids, and terpenoids (*18*, *19*). The major constituents are flavonoids of which mono-, di-, and tri-glycosides and coumaric acid esters that are based on the flavonols kaempferol and quercetin dominate. Lesser quantities of glycosides are derived from isorhamnetin, myricetin, and 3′-methylmyricetin. Nonglycosidic biflavonoids, catechins, and proanthocyanidins are also present (*15*). Characteristic constituents of this plant material are the unique diterpene lactones ginkgolides A, B, C, J, and M and the sesquiterpene lactone bilobalide (*17*). Representative structures of the major and characteristic constituents are presented below.

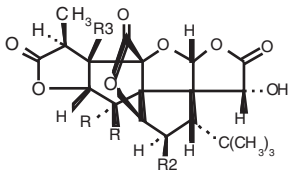


	R1	R2	R3	R4
amentoflavone	O	OH	OH	H
bilobetin	OCH_3	OH	OH	H
ginkgetin	OCH_3	OCH_3	OH	H
isoginkgetin	OCH_3	OH	OCH_3	H
5'-methoxybilobetin	OCH_3	OH	OH	OCH_3
sciadopitysin	OCH_3	OCH_3	OCH_3	H

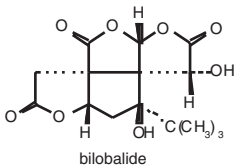




(R = H , OH , OC_3)
flavonoid glycosides



	R	R'	R2	R3
ginkgolide A	H	H	H	OH
ginkgolide B	H	OH	H	OH
ginkgolide C	OH	H	OH	OH
ginkgolide J	H	H	OH	OH
ginkgolide M	OH	H	OH	H



bilobalide

Dosage forms

Standardized extracts (dry extracts from dried leaves, extracted with acetone and water, drug:extract ratio 35–67:1) contain 22–27% flavone glycosides and 5–7% terpene lactones, of which approximately 2.8–3.4% consists of ginkgolides A, B, and C and 2.6–3.2% bilobalide. The level of ginkgolic acids is below 5 mg/kg. Coated tablets and solution for oral administration are prepared from standardized purified extracts (*20*, *21*).

Medicinal uses

Uses supported by clinical data

Extracts as described above (Dosage forms) have been used for symptomatic treatment of mild to moderate cerebrovascular insufficiency (demential syndromes in primary degenerative dementia, vascular dementia, and mixed forms of both) with the following symptoms: memory deficit, disturbance in concentration, depressive emotional condition, dizziness, tinnitus, and headache (*1*, *3*, *20–22*). Such extracts are also used to improve pain-free walking distance in people with peripheral arterial occlusive disease such as intermittent claudication, Raynaud disease, acrocyanosis, and post-phlebitis syndrome, and to treat inner ear disorders such as tinnitus and vertigo of vascular and involutive origin (*20*, *23–27*). Extracts and doses other than those described in Dosage forms and Posology are used for similar but milder indications (*28*, *29*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

As a vermifuge, to induce labour, for the treatment of bronchitis, chronic rhinitis, chilblains, arthritis, and oedema (*3*, *5*).

Pharmacology

Experimental pharmacology

Cerebrovascular insufficiency and peripheral vascular diseases

In vitro studies. A standardized extract of *Ginkgo biloba* (100 μg/ml) did not produce isometrically recordable contractions in isolated rabbit aorta but did potentiate the contractile effect of norepinephrine (*30*). Higher concentrations ($EC_{50} \approx 1.0$ mg/ml) produced a concentration-dependent contraction that could be antagonized by the α-adrenoceptor-blocking agent phentolamine (*30*). Both cocaine and desipramine, inhibitors of catecholamine re-uptake, potentiated the contractile effect of norepinephrine but inhibited the contractile effects of a

standardized extract of *G. biloba* and tyramine (*30*). The results of these experiments indicate that the contractile action of *G. biloba* may be due to the release of catecholamines from endogenous tissue reserves, and this activity may explain some of the therapeutic effects of the drug in humans (e.g. improvement in cerebrovascular and peripheral vascular insufficiency) (*1, 30*). On the basis of experiments comparing the effects of an extract of *G. biloba*, phentolamine, propranolol, gallopamil, theophylline, and papaverine on the biphasic contractile response of norepinephrine in isolated rat aorta, researchers concluded that *G. biloba* had musculotropic action similar to that of papaverine (*31*). This activity was previously reported for the flavonoids quercetin, kaempferol, and isorhamnetin, isolated from the leaves of *G. biloba* (*32*). The flavonoids and papaverine both inhibit 3′,5′-cyclic-GMP phosphodiesterase, which in turn induces endothelium-dependent relaxation in isolated rabbit aorta by potentiating the effects of endothelium-derived relaxing factors (*1*).

In vitro studies have demonstrated that *G. biloba* extracts scavenge free radicals (*33–37*). *Ginkgo biloba* extracts have been reported to reduce free radical-lipid peroxidation induced by NADPH-Fe^{3+} systems in rat microsomes (*33*), and to protect human liver microsomes from lipid peroxidation caused by ciclosporin A (*34*). The extract also inhibits the generation of reactive oxygen radicals in human leukocytes treated with phorbol myristate acetate (*35*). The antioxidant action of *G. biloba* extract may prolong the half-life of endothelium-derived relaxing factor by scavenging superoxide anions (*36, 37*). Both the flavonoid and terpenoid constituents of *G. biloba* appear to aid the free-radical scavenging activity of the drug (*37*).

Ginkgo biloba extract protected against brain tissue hypoxic damage *in vitro*. The ginkgolides and bilobalide were responsible for the antihypoxic activity of the extract (*38, 39*). Ginkgolides A and B have been shown to protect rat hippocampal neurons against ischaemic damage, which may be due to their ability to act as antagonists to receptors for platelet-activating factor (PAF) (*40–42*).

In vivo studies. Oral administration of *G. biloba* extract protected rats against induced cerebral ischaemia (*43–45*). Intravenous perfusion of a *G. biloba* extract prevented the development of multiple cerebral infarction in dogs injected with fragments of an autologous clot into a common carotid artery (*46*). These data suggest that *G. biloba* extract, administered after clot formation, may have some beneficial effects on acute cerebral infarction or ischaemia caused by embolism (*1*). Other experiments demonstrated that animals treated with *G. biloba* extract survived under hypoxic conditions longer than did untreated controls (*47, 48*). Longer survival was due not only to significant improvements in cerebral blood flow, but also to an increase in the level of glucose and ATP (*44, 48–50*). Other studies have shown that a *G. biloba* extract devoid of ginkgolides but containing bilobalide had protective activity when administered intraperitoneally to mice with induced hypobaric hypoxia (*51, 52*). Intravenous infusion of *G. biloba* extract significantly increased pial arteriolar diameter in cats (*53*) and improved

cerebral blood flow in rats (*53*). The active constituents of *G. biloba* responsible for increasing cerebral blood flow appeared to be the non-flavonoid compounds (*54*); ginkgolide B may be responsible for this action owing to its PAF-antagonist activity (*55*, *56*). Furthermore, intravenous administration of a standardized *G. biloba* extract and ginkgolide B to rats showed that the extract, but not ginkgolide B, decreased the brain's use of glucose (*57*).

The constituents of *G. biloba* responsible for its anti-ischaemic activity remain undefined. The flavonoids, ginkgolides, and bilobalide have all been suggested, but it is possible that other constituents may be responsible.

An extract of *G. biloba* was effective in the *in vivo* treatment of cerebral oedema, a condition of excessive hydration of neural tissues owing to damage by neurotoxic agents (such as triethyltin) or trauma (*58–60*). Bilobalide appeared to play a significant role in the antioedema effect (*61*, *62*). Oral or subcutaneous administration of an extract of *G. biloba* to rats with acute and chronic phases of adriamycin-induced paw inflammation partially reversed the increase in brain water, sodium, and calcium and the decrease in brain potassium associated with sodium arachidonate-induced cerebral infarction (*63*).

Mice treated with a standardized extract of *G. biloba* (100 mg/kg, orally for 4–8 weeks) showed improved memory and learning during appetitive operant conditioning (*64*).

Vestibular and auditory effects

Ginkgo biloba extract improved the sum of action potentials in the cochlea and acoustic nerve in cases of acoustically produced sound trauma in guinea-pigs (*1*, *65*). The mechanism reduced the metabolic damage to the cochlea. Oral or parenteral administration of a standardized *G. biloba* extract to mice (2 mg/kg) improved the ultrastructure qualities of vestibular sensory epithelia when the tissue was fixed by vascular perfusion (*66*). Improvement was due to the effects of the drug on capillary permeability and general microcirculation (*1*, *66*).

Positive effects on vestibular compensation were observed after administration of *G. biloba* extract (50 mg/kg intraperitoneally) to rats and cats that had undergone unilateral vestibular neurectomy (*67*, *68*).

Antagonism of platelet-activating factor (PAF)

The ginkgolides, and in particular ginkgolide B, are known antagonists of PAF (*69–73*). PAF is a potent inducer of platelet aggregation, neutrophil degranulation, and oxygen radical production leading to increased microvascular permeability and bronchoconstriction. Intravenous injections of PAF induced transient thrombocytopenia in guinea-pigs, which was accompanied by non-histamine-dependent bronchospasm (*69*, *70*). Ginkgolide B has been shown to be a potent inhibitor of PAF-induced thrombocytopenia and bronchoconstriction (*71*, *72*). PAF or ovalbumin-induced bronchoconstriction in sensitized guinea-pigs was inhibited by an intravenous injection of ginkgolide B (1–3 mg/kg) 5 minutes prior to challenge (*73*).

Clinical pharmacology

Cerebral insufficiency

Cerebral insufficiency is an inexact term to describe a collection of symptoms associated with dementia (*21*, *22*). In dementia owing to degeneration with neuronal loss and impaired neurotransmission, decline of intellectual function is associated with disturbances in the supply of oxygen and glucose. In clinical studies *G. biloba* effectively managed symptoms of cerebral insufficiency including difficulty in concentration and memory, absent-mindedness, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus, and headache (*20–22*). Several mechanisms of action of *G. biloba* have been described: effects on blood circulation such as the vasoregulating activity of arteries, capillaries, veins (increased blood flow); rheological effects (decreased viscosity, by PAF-receptor antagonism); metabolic changes such as increased tolerance to anoxia; beneficial influence on neurotransmitter disturbances; and prevention of damage to membranes by free radicals (*22*). Treatment of humans with *G. biloba* extract has been shown to improve global and local cerebral blood flow and microcirculation (*74–76*), to protect against hypoxia (*77*), to improve blood rheology, including inhibition of platelet aggregation (*74*, *78–81*), to improve tissue metabolism (*82*), and to reduce capillary permeability (*83*).

A critical review of 40 published clinical trials (up to the end of 1990) using an orally administered *G. biloba* extract in the treatment of cerebral insufficiency concluded that only eight of the studies were well performed (*21*, *22*). Almost all trials reported at least a partially positive response at dosages of 120–160 mg a day (standardized extract) and treatment for at least 4–6 weeks (*21*, *22*). In a comparison of *G. biloba* with published trials using co-dergocrine (dihydroergotoxine), a mixture of ergoloid mesilates used for the same purpose, both *G. biloba* extract and co-dergocrine showed similar efficacy. A direct comparison of 120 mg of *G. biloba* standardized extract and 4.5 mg co-dergocrine showed similar improvements in both groups after 6 weeks (*84*).

A meta-analysis of 11 placebo-controlled, randomized double-blind studies in elderly patients given *G. biloba* extract (150 mg orally per day) for cerebral insufficiency concluded that eight studies were well performed (*85*). Significant differences were found for all analysed single symptoms, indicating the superiority of the drug in comparison with the placebo. Analysis of the total score of clinical symptoms indicated that seven studies confirmed the effectiveness of *G. biloba* extract, while one study was inconclusive (*85*).

Peripheral arterial occlusive disease

The effectiveness of *G. biloba* extract in the treatment of intermittent claudication (peripheral arterial occlusive disease Fontaine stage II), as compared with a placebo, was demonstrated in placebo-controlled, double-blind clinical trials by a statistically significant increase in walking distance (*1*, *23*, *24*). Sixty patients with peripheral arterial occlusive disease in Fontaine stage IIb

who were treated with the drug (120–160 mg for 24 weeks) and underwent physical training also clearly increased their walking distance (*25*).

Out of 15 controlled trials (up to the end of 1990) only two (*23*, *24*) were of acceptable quality (*22–24*). The results of both studies were positive and showed an increase in walking distance in patients with intermittent claudication after 6 months (*23*), and an improvement of pain at rest in patients treated with 200 mg of *G. biloba* extract for 8 weeks (*24*).

After meta-analysis of five placebo-controlled clinical trials (up to the end of 1991) of *G. biloba* extract in patients with peripheral arterial disease, investigators concluded that the extract exerted a highly significant therapeutic effect (*26*).

Vertigo and tinnitus

Ginkgo biloba extracts have been used clinically in the treatment of inner ear disorders such as hearing loss, vertigo, and tinnitus. In a placebo-controlled, double-blind study of 68 patients with vertiginous syndrome of recent onset, treatment with *G. biloba* extract (120–160 mg daily, for 4–12 weeks) produced a statistically significant improvement as compared with the placebo group (*27*).

The results of clinical studies on the treatment of tinnitus have been contradictory. At least six clinical studies have assessed the effectiveness of *G. biloba* extract for the treatment of tinnitus. Three studies reported positive results (*86*, *87*, *88*). One multicentre, randomized, double-blind, 13-month study of 103 patients with tinnitus showed that all patients improved, irrespective of the prognostic factor, when treated with *G. biloba* extract (160 mg/day for 3 months) (*86*). Three other clinical trials reported negative outcomes (*89–91*). Statistical analysis of an open study (80 patients) without placebo, coupled with a double-blind, placebo-controlled part (21 patients), demonstrated that a concentrated *G. biloba* extract (29.2 mg/day for 2 weeks) had no effect on tinnitus (*91*).

Contraindications

Hypersensitivity to *G. biloba* preparations (*20*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Investigations with *G. biloba* extracts have shown no effects that were mutagenic, carcinogenic, or toxic to reproduction (*20*).

Pregnancy: non-teratogenic effects

The safety of Folium Ginkgo for use during pregnancy has not been established.

Nursing mothers

Excretion of Folium Ginkgo into breast milk and its effects on the newborn have not been established.

Other precautions

No information is available concerning general precautions or drug interactions, drug and laboratory test interactions, teratogenic effects on pregnancy, or paediatric use.

Adverse reactions

Headaches, gastrointestinal disturbances, and allergic skin reactions are possible adverse effects (*20*).

Posology

Dried extract (as described in Dosage forms), 120–240 mg daily in 2 or 3 divided doses (*2*); 40 mg extract is equivalent to 1.4–2.7 g leaves (*20*). Fluid extract (1 : 1), 0.5 ml 3 times a day (*1*, *2*).

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Radix Ginseng

Definition

Radix Ginseng is the dried root of *Panax ginseng* C.A. Meyer (Araliaceae) (*1–5*).[1]

Synonyms

Panax schinseng Nees (*2*).

Other *Panax* species, including *P. quinquefolius* L. (American ginseng), *P. notoginseng* Burk. (San-chi ginseng), *P. pseudoginseng* Wall. ssp. *japonicus* Hara = *P. japonicus* C.A. Meyer (Japanese chikutsu ginseng) and *P. notoginseng* ssp. *himalaicus* (Himalayan ginseng) have also been referred to as "ginseng" and used medically (*6*, *7*). However, scientific documentation of these species is insufficient to justify the preparation of a monograph at this time.

Selected vernacular names

Chosen ninjin, ginseng, Ginsengwurzel, hakusan, hakushan, higeninjin, hongshen, hungseng, hungshen, hunseng, jenseng, jenshen, jinpi, kao-li-seng, korean ginseng, minjin, nhan sam, ninjin, ninzin, niuhuan, Oriental ginseng, otane ninjin, renshen, san-pi, shanshen, sheng-sai-seng, shenshaishanshen, shengshaishen, t'ang-seng, tyosenninzin, yakuyo ninjin, yakuyo ninzin, yeh-shan-seng, yuan-seng, yuanshen (*1*, *2*, *4–10*).

Description

A perennial herb with characteristic branched roots extending from the middle of the main root in the form of a human figure. Stem erect, simple, and not branching. Leaves verticillate, compound, digitate, leaflets 5, with the 3 terminal leaflets larger than the lateral ones, elliptical or slightly obovate, 4–15 cm long by 2–6.5 cm wide; apex acuminate; base cuneate; margin serrulate or finely bidentate. In general, 1 leaf in the first year with 1 leaflet added annually until the sixth year. Inflorescence a small terminal umbel, hemispherical in early summer. Flowers polygamous, pink. Calyx vaguely 5-toothed. Petals 5, stamens 5. Fruit a small berry, nearly drupaceous, and red when ripe in autumn (*8*).

[1] Steamed *Panax ginseng* root is listed in the Japanese pharmacopoeia as "Red Ginseng (Ginseng Radix Rubra)" (*2*).

Plant material of interest: dried root

General appearance

The main root is fusiform or cylindrical, 2.5–20 cm long by 0.5–3.0 cm in diameter; externally greyish yellow; upper part or entire root exhibiting sparse, shallow, interrupted, and coarse transverse striations and distinct longitudinal wrinkles; lower part bearing 2–5 branching lateral roots and numerous slender rootlets with inconspicuous minute tubercles. Rhizomes 1–4 cm long by 0.3–1.5 cm in diameter, mostly constricted and curved, bearing adventitious roots and sparse depressed circular stem scars. Texture relatively hard, fracture yellowish white, cambium ring brownish yellow, starchy (*1–5*).

Organoleptic properties

Colour, greyish white to amber-yellow; odour, characteristic; taste, slightly sweet at first, followed by a slight bitterness (*1*, *2*).

Microscopic characteristics

The transverse section shows cork consisting of several rows of cells; cortex narrow; phloem showing clefts in the outer part, and parenchymatous cells densely arranged and scattered with resin canals containing yellow secretions in the inner part; cambium in a ring; xylem rays broad, vessels singly scattered or grouped in an interrupted radial arrangement, and occasionally accompanied by non-lignified fibres; parenchyma cells containing abundant starch grains and a few clusters of calcium oxalate (*1*, *3–5*).

Powdered plant material

Yellowish white; fragments of resin canals containing yellow secretions; clusters of calcium oxalate (20–68 μm in diameter), few, with acute angles; cork cells subsquare or polygonal, with thin and sinuous walls; reticulate and scalariform vessels 10–56 μm in diameter; starch granules fairly abundant, simple, subspheroidal, semicircular, or irregular polygonal (4–30 μm in diameter), singly or in groups of two to four (*1–5*).

Geographical distribution

Mountain regions of China (Manchuria), the Democratic People's Republic of Korea, Japan, the Republic of Korea, and the Russian Federation (eastern Siberia) (*7*, *8*). It is commercially produced mainly by cultivation (*6*).

General identity tests

Macroscopic and microscopic examinations, microchemical tests, and thin-layer chromatographic analysis (*1–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Ginseng products should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 2% (*2*, *3*).

Total ash

Not more than 4.2% (*2*).

Acid-insoluble ash

Not more than 1% (*4*).

Sulfated ash

Not more than 12% (*5*).

Alcohol-soluble extractive

Not less than 14.0% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Ginseng is not more than 0.05 mg/kg (*13*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*14*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

Chemical and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

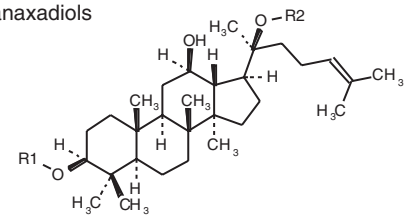
Microchemical, thin-layer chromatographic, and spectrophotometric methods are used for the qualitative and quantitative analysis of ginsenosides (*1–5*). High-performance liquid chromatography (*15–17*) and liquid chromatography–mass spectrometry (*18*) methods are also available.

Characteristic saponins known as ginsenosides, not less than 1.5% calculated as ginsenoside Rg_1 (D-glucopyranosyl-6β-glucopyranosyl-20*S*-protopanaxatriol, relative molecular mass 800) (*3*, *5*).

Major chemical constituents

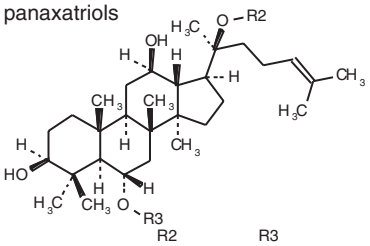
The major chemical constituents are triterpene saponins. More than 30 are based on the dammarane structure, and one (ginsenoside Ro) is derived from oleanolic acid (*6*, *7*, *17*, *19*). The dammarane saponins are derivatives of either protopanaxadiol or protopanaxatriol. Members of the former group include ginsenosides Ra_{1-3}, Rb_{1-3}, Rc, Rc_2, Rd, Rd_2, and Rh_2; (20*S*)-ginsenoside Rg_3; and malonyl ginsenosides Rb_1, Rb_2, Rc, and Rd. Examples of protopanaxatriol saponins are ginsenosides Re_2, Re_3, Rf, Rg_1, Rg_2, and Rh_1; 20-gluco-ginsenoside Rf; and (20*R*)-ginsenosides Rg_2 and Rh_1. Those considered most important are ginsenosides Rb_1, Rb_2, Rc, Rd, Rf, Rg_1, and Rg_2; Rb_1, Rb_2, and Rg_1 are the most abundant. Representative structures are presented below.

panaxadiols



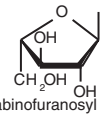
	R1	R2
ginsenoside Rb_1	*O*-glc-(1→2)-glc-	*O*-glc-(1→6)-glc-
ginsenoside Rb_2	*O*-glc-(1→2)-glc-	*O*-ara(p)-(1→6)-glc-
ginsenoside Rc	*O*-glc-(1→2)-glc-	*O*-ara(f)-(1→6)-glc-
ginsenoside Rd	*O*-glc-(1→2)-glc-	glc-

panaxatriols



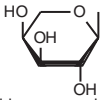
	R2	R3
ginsenoside Re	glc-	*O*-rha-(1→2)-glc-
ginsenoside Rf	H-	*O*-glc-(1→2)-glc-
ginsenoside Rg_1	glc-	glc-
ginsenoside Rg_2	H-	*O*-rha-(1→2)-glc-

ara(f)-



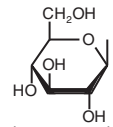
α-L-arabinofuranosyl

ara(p)-



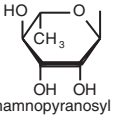
α-L-arabinopyranosyl

glc-



β-D-glucopyranosyl

rha-



α-L-rhamnopyranosyl

Dosage forms

Crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges. Store in a cool, dry place in well-sealed containers (*20*).

Medicinal uses

Uses supported by clinical data

Radix Ginseng is used as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness, and loss of concentration, and during convalescence (*21–29*).

Uses described in pharmacopoeias and in traditional systems of medicine

Radix Ginseng has been used clinically in the treatment of diabetes (*1*), but further clinical studies are needed. The drug is also used in the treatment of impotence, prevention of hepatotoxicity, and gastrointestinal disorders such as gastritis and ulcers (*1*, *7*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of liver disease, coughs, fever, tuberculosis, rheumatism, vomiting of pregnancy, hypothermia, dyspnoea, and nervous disorders (*7*).

Pharmacology

Experimental pharmacology

The suggested mode of action of Radix Ginseng is twofold. First, the drug has an "adaptogenic" effect (*30*), which produces a non-specific increase in the body's own defences against exogenous stress factors and noxious chemicals (*31*). Secondly, the drug promotes an overall improvement in physical and mental performance (*30–33*).

Treatment of cultured mammalian cells, isolated organs, and animal models (primarily mice and rats) with Radix Ginseng before or during exposure to physical, chemical, or psychological stress increased the ability of the respective model systems to resist the damaging effects of various stressors (*31*). These results were demonstrated in cases of radiation poisoning (*34–36*), viral infection and tumour load (*37*, *38*), alcohol or carbon tetrachloride poisoning (*39–41*), oxygen deprivation and hypobaric pressure (*42*, *43*), light or temperature stress, emotional stress, and electrical shock or restricted movement (*44*, *45*, *46*). The mechanism by which the drug exerts its activity is most likely through the hypothalamus–pituitary–adrenal axis (*47–49*) and through its immunostimulant effect (*50*).

Intraperitoneal administration to rats of ginseng saponin fractions or the ginsenosides Rb_1, Rb_2, Rc, Rd, and Re elevated serum levels of adrenocorticotropic hormone (ACTH) and corticosterone (*51*, *52*). Pretreatment with dexamethasone, which blocks hypothalamus and pituitary functions, prevented ginseng saponin-mediated release of ACTH and corticosterone, and thereby demonstrated that the increase in serum corticosterone by ginseng occurs indirectly through release of ACTH from the pituitary (*51*, *52*).

The immunomodulatory activity of ginseng appears to be at least partly responsible for its adaptogenic effect (*50*, *53*, *54*). Alcohol extracts of Radix Ginseng stimulated phagocytosis *in vitro*, were mitogenic in cultured human lymphocytes, stimulated the production of interferon, and enhanced the activity of natural killer cells (*55*, *56*). Intraperitoneal administration of an extract of the drug to mice stimulated cell-mediated immunity against Semliki Forest virus, elevated antibody levels against sheep red blood cells and natural killer cells (*57*), and stimulated the production of interferon (*58*).

Improvement in physical and mental performance has been observed in mice and rats after oral or intraperitoneal administration of the drug (*59–63*). Oral administration of ginseng saponin fractions to mice increased endurance and prolonged swimming time in swimming tests (*63*). However, two studies concluded that ginseng had no positive effects on the physical performance in mice and rats (*64*, *65*). The adaptogenic effects of Radix Ginseng are generally attributed to the ginsenosides (*66*, *67*). The ginsenosides have been shown to alter mechanisms of fuel homeostasis during prolonged exercise, by increasing the capacity of skeletal muscle to oxidize free fatty acids in preference to glucose for cellular energy production (*59*). Other constituents of Radix Ginseng, such as vanillic and salicylic acid, have also been reported to have "antifatigue" activity in rats (*68*). Furthermore, the antioxidant activity of ginseng was associated with both the ginsenosides and the flavonoid constituents (*31*, *69*). The ginsenosides protected pulmonary vascular endothelium against free-radical-induced injury (*69*).

Mice given ginseng extract or ginsenosides Rb_1 and Rg_2 orally during passive avoidance response tests showed an improvement in learning ability which was negatively influenced by stress (*30*), and rats showed improved retention of learned behaviour (*70*). Ginsenosides Rg_1 and Rb_1 are the active nootropic constituents of the drug (*66*), and improve memory and learning in normal as well as cognition-impaired animals. The mode of action involves an increase in the synthesis and release of acetylcholine, and a decrease of brain serotonin levels (*66*). In cerebral and coronary blood vessels, extracts of Radix Ginseng produced vasodilatation, which improved brain and coronary blood flow (*71*). The vasodilatory activity of the ginsenosides appears to be primarily due to relaxation of vascular smooth muscles. The ginsenosides block the constricting effects of norepinephrine in isolated aorta strips, and inhibit the uptake of $^{45}Ca^{2+}$ in the membrane and sarcolemma of rabbit heart tissue. Inhibition of Ca^{2+} uptake in the muscle membrane contributes to the mechanism of vasodilatation (*71*).

A number of polypeptides and glycans isolated from Radix Ginseng, named GP and panaxans A–E, respectively, have demonstrated hypoglycaemic activity when given intraperitoneally to mice (*72*, *73*). Two of the glycans, panaxans A and B, have been shown to stimulate hepatic glucose utilization by increasing the activity of glucose-6-phosphate 1-dehydrogenase, phosphorylase *a*, and phosphofructokinase (*72*). Panaxan A did not affect plasma insulin levels or insulin sensitivity, but panaxan B elevated the plasma insulin level by stimulating insulin secretion from pancreatic islets, and further enhanced insulin sensitivity by increasing insulin binding to receptors (*72*). The panaxans are not active after oral administration. Administration of GP (intravenously or subcutaneously) to mice or rats decreased blood glucose and liver glycogen levels (*73*). Radix Ginseng also contains a number of other constituents with hypoglycaemic activity (*72*, *74*). Adenosine, isolated from a water extract of Radix Ginseng, enhanced lipogenesis and cyclic AMP accumulation of adipocytes, and some of the ginsenosides inhibited ACTH-induced lipolysis, suppressed insulin-stimulated lipogenesis, and stimulated the release of insulin from cultured islets (*72*).

Subcutaneous administration of a ginseng extract enhanced the mating behaviour of male rats (*75*). The drug further stimulated spermatogenesis in rat (*76*), and rabbit testes, and increased the motility and survival of rabbit sperm outside the body (*75*).

Intragastric or intradermal administration of an ethanol extract of the drug to rats decreased histamine-, pentagastrin-, carbachol- and vagal stimulation-induced gastric secretion, and inhibited gastric ulcers induced by stress or by pyloric ligation (*77–79*).

Liver-protectant activity of ginseng has been demonstrated *in vitro* and *in vivo* (*80*, *81*). Intraperitoneal administration of Radix Ginseng extracts to normal and dexamethasone-treated rats did not influence the blood chemistry of normal rats, but it decreased aspartate aminotransferase and alanine aminotransferase levels in dexamethasone-treated animals, thereby demonstrating a liver-protectant effect (*81*). However, another study demonstrated that an intraperitoneal injection of a methanol extract of Radix Ginseng had no protective activity against carbon tetrachloride-induced hepatotoxicity in rats (*82*).

Clinical pharmacology

Antifatigue activity

The results of clinical studies measuring increased performance and antifatigue effects of ginseng extracts are conflicting and, in general, most studies suffer from poor methodology, lack of proper controls, and no standardization of the ginseng extracts used. The influence of chronic Radix Ginseng administration (2 g/day orally for 4 weeks) on substrate utilization, hormone production, endurance, metabolism, and perception of effort during consecutive days of exhaustive exercise in 11 naval cadets was reported. No significant differences

were observed between the control group and the group receiving the ginseng supplementation (*83*). Another clinical trial with eight participants reported no significant difference between placebo and ginseng administration during exhaustive exercise after 7 days of treatment (*84*). A randomized, double-blind, cross-over study sought the effects of ginseng on circulatory, respiratory, and metabolic functions during maximal exercise in 50 men (21–47 years old) (*24*). Total tolerated workload and maximal oxygen uptake were significantly higher following ginseng administration than with placebo. At the same workload, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production, and heart rate during exercise were all lower in the ginseng treatment group. The results indicated that the ginseng preparations effectively increased the work capacity of the participants by improving oxygen utilization (*24*). A placebo-controlled, cross-over study determined the effects of ginseng on the physical fitness of 43 male triathletes (*25*). The participants received 200 mg of a ginseng preparation twice daily for two consecutive training periods of 10 weeks. No significant changes were observed during the first 10-week period, but ginseng appeared to prevent the loss of physical fitness (as measured by oxygen uptake and oxygen pulse) during the second 10-week period (*25*). Two further studies with athletes given 100 mg of a standardized ginseng extract twice daily for 9 weeks reported significant improvement in aerobic capacity and reduction in blood lactate and heart rates (*26*, *27*), but placebos or controls were not used in either of the two studies. Further extension of these studies using placebo-controlled, double-blind trials demonstrated significant improvement in the ginseng group as compared with the placebo group (*28*). Similar results were reported in another study on athletes, and the differences between the ginseng and placebo groups lasted for approximately 3 weeks after the last ginseng dose (*29*). The effects of 1200 mg of Radix Ginseng in a placebo-controlled, double-blind cross-over study in fatigued night nurses were assessed and the results were compared with placebo and with effects on nurses engaged in daytime work (*22*). Ginseng restored ratings on tests of mood, competence, and general performance, and the study concluded that ginseng had anti-fatigue activity (*22*).

Aqueous and standardized ginseng extracts were tested in a placebo-controlled, double-blind study for immunomodulatory actions (*85*). Sixty healthy volunteers were divided into three groups of 20 each and were given either a placebo or 100 mg of aqueous ginseng extract or 100 mg of standardized ginseng extract, every 12 hours for 8 weeks. Blood samples drawn from the volunteers revealed an increase in chemotaxis of polymorphonuclear leukocytes, the phagocytic index, and the total number of T3 and T4 lymphocytes after 4 and 8 weeks of ginseng therapy, as compared with the placebo group. The group receiving the standardized extract also increased their T4:T8 ratio and the activity of natural killer cells. The conclusion of this study was that ginseng extract stimulated the immune system in humans, and that the standardized extract was more effective than the aqueous extract (*85*).

Psychomotor activity

A double-blind, placebo-controlled clinical study assessed the effect of standardized ginseng extract (100 mg twice daily for 12 weeks) on psychomotor performance in 16 healthy individuals (*23*). Various tests of pyschomotor performance found a favourable effect on attention, processing, integrated sensory–motor function, and auditory reaction time. The study concluded that the drug was superior to the placebo in improving certain psychomotor functions in healthy subjects (*23*).

Antidiabetic activity

Radix Ginseng has been shown in clinical studies to have beneficial effects in both insulin-dependent and non-insulin-dependent diabetic patients (*86*, *87*). Oral administration of ginseng tablets (200 mg daily for 8 weeks) to 36 non-insulin-dependent patients elevated mood, improved physical performance, reduced fasting blood glucose and serum aminoterminal propeptide of type III procollagen concentrations, and lowered glycated haemoglobin (*87*).

Impotence

Ginseng extracts improved sperm production in men and may have some usefulness in treating impotence (*32*). The ginsenosides, which appear to be the active components, are thought to depress blood prolactin levels, thereby increasing libido (*32*). In one clinical study, 90 patients with erectile dysfunction were treated with ginseng saponins (600 mg orally per day). Treatment improved rigidity, tumescence, and libido, but not the frequency of coitus (*88*).

Contraindications

None (*21*, *50*, *89*, *90*).

Warnings

No information available.

Precautions

General

Diabetic patients should consult a physician prior to taking Radix Ginseng, as ginseng intake may slightly reduce blood glucose levels (*86*, *87*).

Drug interactions

There are two reports of an interaction between Radix Ginseng and phenelzine, a monoamine oxidase inhibitor (*91*, *92*). The clinical significance of this interaction has not been evaluated.

Drug and laboratory test interactions

None reported.

Carcinogenesis, mutagenesis, impairment of fertility

Radix Ginseng is not carcinogenic or mutagenic *in vitro*, and does not have any effect on fertility (*90*).

Pregnancy: teratogenic effects

Radix Ginseng is not teratogenic *in vivo* (*90*).

Pregnancy: non-teratogenic effects

The safety of Radix Ginseng for use in pregnancy has not been established.

Nursing mothers

Excretion of Radix Ginseng compounds into breast milk and its effects on the newborn have not been established.

Paediatric use

The safety and efficacy of Radix Ginseng use in children have not been established.

Adverse reactions

Various researchers who studied Radix Ginseng extracts using conventional toxicological methods in five different animal models reported no acute or chronic toxicity of the extract (*89*, *90*, *93*).

On the basis of Radix Ginseng's long use, and the relative infrequency of significant demonstrable side-effects, it has been concluded that the use of Radix Ginseng is not associated with serious adverse effects if taken at the recommended dose (*90*, *93*). However, in Siegel's open study of 133 patients ingesting large quantities, ginseng was reported to result in hypertension, nervousness, irritability, diarrhoea, skin eruptions, and insomnia, which were collectively called ginseng abuse syndrome (GAS) (*94*). Critical analysis of this report has shown that there were no controls or analyses to determine the type of ginseng being ingested or the constituents of the preparation taken, and that some of the amounts ingested were clearly excessive (as much as 15 g per day, where the recommended daily dose is 0.5–2 g) (*50*, *90*, *95*). When the dose was decreased to 1.7 g/day the symptoms of the "syndrome" were rare. Thus the only conclusion that can be validly extracted from the Siegel study is that the excessive and uncontrolled intake of ginseng products should be avoided (*90*). One case of ginseng-associated cerebral arteritis has been reported in a patient consuming a high dose of an ethanol extract of ginseng root (approximately 6 g in one dose) (*96*). However, again the type and quantity of ginseng extract were

not reported. Two cases of mydriasis and disturbance in accommodation, as well as dizziness have been reported after ingestion of large doses (3–9 g) of an unspecified type of ginseng preparation (*97*).

Estrogenic-like side-effects have been reported in both premenopausal and postmenopausal women following the use of ginseng. Seven cases of mastalgia (*98–100*) and one case of vaginal bleeding in a postmenopausal woman (*101*) were reported after ingestion of unspecified ginseng products. An increased libido in premenopausal women has also been reported (*100*). Specific studies on the possible hormonal side-effects of ginseng have been carried out with a standardized ginseng extract (*102–104*). Under physiological conditions, there is no interaction of the ginseng extract with either cytosolic estrogen receptors isolated from mature rat uterus or progesterone receptors from human myometrium (*102*). Furthermore, clinical studies have demonstrated that a standardized ginseng extract does not cause a change in male and female hormonal status (*103*, *104*).

Posology

Unless otherwise prescribed, daily dose (taken in the morning): dried root 0.5–2 g by decoction; doses of other preparations should be calculated accordingly (*21*, *23*, *89*).

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Radix Glycyrrhizae

Definition

Radix Glycyrrhizae consists of the dried roots and rhizomes of *Glycyrrhiza glabra* L. and its varieties (*1–7*) or of *Glycyrrhiza uralensis* Fisch. (*6*, *7*) (Fabaceae).[1]

Synonyms

Liquiritae officinalis Moench is a synonym of *Glycyrrhiza glabra* L. (*1*).

Selected vernacular names

Glycyrrhiza glabra L. and its varieties

Adimaduram, akarmanis, asloosoos, aslussos, athimaduram, athimaduramu, athimathuram, bekh-e-mahak, bois doux, cha em thet, estamee, gancao, glycyrrhiza, herbe aux tanneurs, hsi-pan-ya-kan-tsao, irk al hiel, irk al hilou, irksos, jakyakgamcho-tang, jashtimadhu, jethimadh, jethimadha, kanpo, kanzo, kan-ts'ao, kum cho, Lakritzenwurzel, licorice, licorice root, liquiritiae radix, liquorice, liquorice root, madhuyashti, madhuyashti rasayama, mulathee, muleti, mulhatti, neekhiyu, Persian licorice, racine de reglisse, racine douce, reglisse, reglisse officinalis, rhizoma glycyrrhizae, Russian licorice, Russian liquorice, Russisches Süssholz, si-pei, sinkiang licorice, Spanish licorice, Spanish liquorice, Spanisches Süssholz, Süssholzwurzel, sweet root, sweetwood, ud al sus, velmi, walmee, welmii, xi-bei, yashti, yashtimadhu, yashtimadhukam, yashtomadhu (*1–15*).

Glycyrrhiza uralensis Fisch.

Chinese licorice, Chinese liquorice, gancao, kan-ts'ao, kanzo, kanzoh, licorice root, liquiritiae radix, north-eastern Chinese licorice, saihokukanzoh, tohoku kanzo, tongpei licorice, tung-pei-kan-tsao, Ural liquorice, uraru-kanzo (*14–17*).

[1] *Glycyrrhiza inflata* Bat. is listed in the Chinese pharmacopoeia (*6*). However, literature references to botanical, chemical, and biological studies on this species are rare. Therefore, it has not been included in this monograph.

Description

Glycyrrhiza glabra L. and its varieties

A perennial plant, up to more than 1 m in height, erect, with highly developed stoloniferous roots. Leaves compound, 9–17 alternate imparipinnate leaflets, oblong to elliptical-lanceolate, acute or obtuse; racemes loose, shorter than the leaves or a little longer. Flowers 1 cm long. Flat pods oblong to linear, 1–3 cm long by 6 mm wide, more or less densely echinate glandular, many-seeded or abbreviated, 2- or 3-seeded (*1*, *11*).

Glycyrrhiza uralensis Fisch.

A perennial glandular herb, 30–100 cm high. Stem erect, with short whitish hairs and echinate glandular hairs; the lower part of the stem is woody. Leaves alternate, imparipinnate; leaflets 7–17, ovate-elliptical, 2–5.5 cm long by 1–3 cm wide; apex obtuse-rounded; base rounded; both surfaces covered with glandular hairs and short hairs. Stipules lanceolate. Inflorescence an axillary cluster. Flowers purplish, papilionaceous; calyx villous. Fruit a flat pod, oblong, sometimes falcate, 6–9 mm wide, densely covered with brownish echinate glandular hairs. Seeds 2–8. The root is cylindrical, fibrous, flexible, 20–22 cm long and 15 mm in diameter, with or without cork, cork reddish, furrowed, light yellow inside (*16*).

Plant material of interest: dried root and rhizome

General appearance

Glycyrrhiza glabra L. and its varieties

The commercial variety, *G. glabra* var. *typica* Regel & Herd, known as Spanish liquorice, consists generally of roots and rhizomes in nearly cylindrical pieces, up to 1 m long and 5–20 mm in diameter; externally, the bark is brownish grey to dark brown, longitudinally wrinkled, occasionally bearing small dark buds in rhizomes or small circular or transverse rootlet-scars in roots. The peeled root is yellow, smooth, fibrous, finely striated; fracture, fibrous in the bark and splintery in the wood; internally, bright yellow. A distinct cambium ring separates the yellowish grey bark from the finely radiate yellow wood; central pith, only in rhizomes (*1*, *2*, *7*).

The commercial variety, *G. glabra* var. *glandulifera* (Wald et Kit) Regel & Herd, known as Russian liquorice, consists mainly of roots, in cylindrical pieces somewhat tapering and sometimes longitudinally split; 15–40 cm long, 1–5 cm in diameter. The enlarged crown of the root may attain up to 10 cm in diameter; externally, the unpeeled root purplish brown, somewhat scaly, with stem scars at the top; the peeled root yellowish, coarsely striated; fracture as for Spanish type; internally, yellow, radiating (*1*).

***Glycyrrhiza uralensis* Fisch.**

The roots and rhizomes are cylindrical, fibrous, flexible, 20–100 cm long, 0.6–3.5 cm in diameter, with or without cork. Externally reddish brown or greyish brown, longitudinally wrinkled, furrowed, lenticellate, and with sparse rootlet scars. Texture compact, fracture slightly fibrous, yellowish white, starchy; cambium ring distinct, rays radiate, some with clefts. Rhizomes cylindrical, externally with bud scars, pith present in the centre of fracture (*6*, *7*, *16*, *17*).

Organoleptic properties

Odour slight and characteristic (*1*, *6*, *7*); taste, very sweet (*1*, *6*, *7*, *13*, *15*, *17*).

Microscopic characteristics

In transverse section the cork is thick, brown or purplish brown, formed of several layers of flattened polygonal thin-walled cells; cortex of phelloderm in root somewhat narrow, yellow fibres of parenchyma cells contain isolated prisms of calcium oxalate; phloem, wide, yellow, traversed by numerous wavy parenchymatous medullary rays, 1–8 cells wide and consisting of numerous radial groups of fibres, each surrounded by a crystal sheath of parenchyma cells. Each cell usually contains a prism of calcium oxalate and layers of parenchyma alternating with sieve tissue, the latter occasionally obliterated, appearing as refractive irregular structures; phloem fibres, very long, with very narrow lumen and strongly thickened stratified walls which are cellulosic in the inner part of the phloem and slightly lignified in the outer; xylem, yellow, distinctly radiate; xylem rays, consisting of small pale yellow parenchyma, groups of fibres similar to those of the phloem but more lignified, and surrounded by crystal-sheath, tracheids, and large wide lumen vessels, 80–200 μm in diameter, with thick yellow reticulate walls or with numerous oval bordered pits with slit-shaped openings. Other parenchyma cells contain small round or oval starch granules. Pith, only in rhizome, dark yellow, parenchymatous. Root, with 4-arch primary xylem, no pith and shows 4 broad primary medullary rays, radiating from the centre at right angles to one another. In peeled liquorice, the cork, cortex, and sometimes part of the phloem are absent (*1*).

Powdered plant material

Light yellow in the peeled or brownish yellow or purplish brown in the unpeeled root. Characterized by the numerous fragments of the fibres accompanied by crystal-sheath, the fibres 8–25 μm, mostly 10–15 μm, in diameter; dark yellow fragments of vessels, 80–200 μm in diameter, containing solitary prismatic crystals of calcium oxalate, free or in cells 10–35 μm (mostly 15–25 μm) long; numerous simple oval, round or fusiform starch granules, free or in parenchyma cells, with no striation but occasionally showing hilum, 2–20 μm (mostly about 10 μm) in diameter; cork may be present (*1*, *2*, *7*).

Geographical distribution

Glycyrrhiza glabra

Native to central and south-western Asia and the Mediterranean region (*11*, *12*, *13*). It is cultivated in the Mediterranean basin of Africa, in southern Europe, and in India (*1*, *11*, *12*, *13*).

Glycyrrhiza uralensis

Northern China, Mongolia, and Siberia (*16*, *17*).

General identity tests

Macroscopic, microscopic, and microchemical examinations (*1–7*); and thin-layer chromatographic analysis for the presence of glycyrrhizin (*2–7*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Glycyrrhizae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*18*, *19*, *20*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 7% (*6*, *7*).

Acid-insoluble ash

Not more than 2% (*1–3*, *6*, *7*).

Sulfated ash

Not more than 10% (*2*).

Water-soluble extractive

Not less than 20% (*8*).

Dilute alcohol-soluble extractive

Not less than 25% (*7*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Glycyrrhizae is not

more than 0.05 mg/kg (*20*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*18*) guidelines for predicting dietary intake of pesticide residues (*21*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*18*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*18*).

Other purity tests

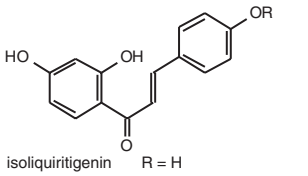
Alcohol-soluble extractive, chemical, and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays

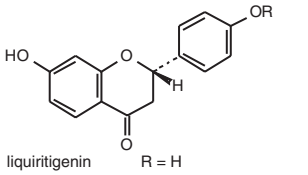
Assay for glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) content (at least 4%) by means of spectrophotometric (*1*, *2*), thin-layer chromatographic–densitometric (*22*, *23*) or high-performance liquid chromatographic (*24–26*) methods.

Major chemical constituents

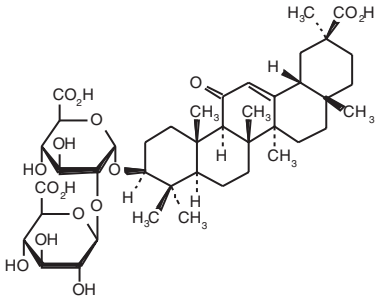
The major constituents are triterpene saponins. Glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) is the major component (2–9%); minor components occur in proportions that vary depending on the species and geographical location (*24–27*). Glycyrrhizin occurs as a mixture of potassium and calcium salts (*9*). It is a monodesmoside, which on hydrolysis releases two molecules of



isoliquiritigenin R = H
isoliquiritin R = β-D-glucopyranosyl



liquiritigenin R = H
liquiritin R = β-D-glucopyranosyl



glycyrrhizin or glycyrrhizic acid or glycyrrhizinic acid

aglycone = glycyrrhetic acid or glycyrrhetinic acid

D-glucuronic acid and the aglycone glycyrrhetic (glycyrrhetinic) acid (enoxolone) (*28*). Glycyrrhizin is generally regarded as the active principle of Radix Glycyrrhizae and is responsible for its sweetness, which is 50 times that of sucrose (*27*). Flavonoid constituents include liquiritigenin and isoliquiritigenin.

Dosage forms

Crude plant material, dried extract and liquid extract. Store in a well-closed container, protected from light and moisture (*1*, *3*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent in the treatment of sore throats, and as an expectorant in the treatment of coughs and bronchial catarrh. Also in the prophylaxis and treatment of gastric and duodenal ulcers, and dyspepsia (*1*, *6*, *8*, *27–29*). As an anti-inflammatory agent in the treatment of allergic reactions (*27*), rheumatism and arthritis (*9*), to prevent liver toxicity, and to treat tuberculosis and adrenocorticoid insufficiency (*9*, *30*).

Uses described in folk medicine, not supported by experimental or clinical data

As a laxative, emmenagogue, contraceptive, galactagogue, antiasthmatic drug, and antiviral agent (*15*). In the treatment of dental caries, kidney stones, heart disease (*15*), "consumption", epilepsy, loss of appetite, appendicitis, dizziness, tetanus, diphtheria, snake bite, and haemorrhoids (*11*, *13*).

Pharmacology

Experimental pharmacology

The demulcent action of the drug is due primarily to glycyrrhizin (*27*). The antitussive and expectorant properties of the drug have also been attributed to glycyrrhizin, which accelerates tracheal mucus secretion (*27*).

The antiulcer activity of Radix Glycyrrhizae has been demonstrated both experimentally and clinically. Intraperitoneal, intraduodenal, or oral administration of aqueous or alcoholic extracts of Radix Glycyrrhizae reduced gastric secretions in rats, and it inhibited the formation of gastric ulcers induced by pyloric ligation, aspirin, and ibuprofen (*27*, *31–32*). Glycyrrhizin and its agly-

cone (glycyrrhetic acid, enoxolone), two of the active constituents of Radix Glycyrrhizae, both have antiphlogistic activity and increase the rate of mucus secretion by the gastric mucosa (*9*). Deglycyrrhizinated liquorice (97% of glycyrrhizin is removed) effectively treated stress-induced ulcers in animal models (*31–34*). The mechanism of antiulcer activity involves acceleration of mucin excretion through increasing the synthesis of glycoprotein at the gastric mucosa, prolonging the life of the epithelial cells, and antipepsin activity (*32*).

The spasmolytic activity of Radix Glycyrrhizae has been demonstrated *in vivo* (guinea-pig, rabbit, and dog) (*35–37*), and appears to be due to the flavonoids liquiritigenin and isoliquiritigenin (*38*).

Glycyrrhizin reduces the toxic action of carbon tetrachloride- and galactosamine-induced cytotoxicity in cultured rat hepatocytes, through its antioxidant activity (*9*, *27*). Glycyrrhizin inhibited histamine release from rat mast cells and prevented carbon tetrachloride-induced liver lesions and macrophage-mediated cytotoxicity (*27*). Intragastric administration of a flavonoid fraction isolated from Radix Glycyrrhizae to mice protected against carbon tetrachloride hepatotoxicity (*39*). Glycyrrhizin protected the liver apparently through its membrane stabilization effects (*27*).

The anti-inflammatory and antiallergic actions of the drug have been attributed to the corticosteroid-like activity of glycyrrhizin and glycyrrhetic acid (enoxolone). These compounds act indirectly by potentiating the activity of corticosteroids. *In vitro*, glycyrrhetic acid inhibits Δ^4 β-reductase, an enzyme that competitively inactivates steroid hormones, and 11β-hydroxysteroid dehydrogenase, the enzyme that deactivates cortisol (*27*). Glycyrrhizin given intraperitoneally suppressed contact dermatitis in mice, and was more effective than prednisolone, but no effects were observed after oral administration (*9*).

In vitro, the drug inhibits the growth of *Bacillus subtilis (*40*)*, *Mycobacterium tuberculosis* (*41*), *Aspergillus spp*. *(*42*)*, *Staphylococcus aureus*, *Mycobacterium smegmatis*, and *Candida albicans* (*43*).

Clinical pharmacology

Oral administration of Radix Glycyrrhizae to 15 patients with peptic ulcer reduced symptoms and improved healing in 75% of the cases (*44*). Glycyrrhetic acid (enoxolone), the active constituent, produced its antiulcer activity by inhibiting 15-hydroxyprostaglandin dehydrogenase and Δ^{13}-prostaglandin reductase (*45*). Inhibition of these two enzymes stimulated an increase in the concentration of prostaglandins E and $F_{2\alpha}$ in the stomach, which promoted the healing of peptic ulcers owing to a cytoprotective effect on the gastric mucosa (*45*). Carbenoxolone, a derivative of glycyrrhetic acid, has been used clinically for years in the treatment of gastric and duodenal ulcers (*46*).

Oral administration of deglycyrrhizinated liquorice (380 mg, 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antacid or cimetidine treatments (*47*). These results indicate that, in addition to

glycyrrhetic acid, other unidentified constituents of Radix Glycyrrhizae contribute to its antiulcer activity.

Reports on the usefulness of liquorice extracts on body fluid homeostasis in patients with Addison disease are contradictory. One study found no positive effects (*48*), while three other studies noted an increase in weight gain and sodium retention (*49–51*).

Contraindications

Radix Glycyrrhizae is contraindicated in patients with hypertension, cholestatic disorders or cirrhosis of the liver, hypokalaemia, or chronic renal insufficiency, and during pregnancy (*9*, *29*).

Warnings

Prolonged use of large doses (>50 g/day) of the drug for extended periods (>6 weeks) may increase water accumulation, causing swelling of the hands and feet. Sodium excretion is reduced and potassium excretion is increased. Blood pressure may rise.

Precautions

General

Radix Glycyrrhizae should not be taken concurrently with corticosteroid treatment. If sore throat or cough persists for more than 3 days, the patient should consult a physician.

Drug interactions

Because it increases potassium loss, Radix Glycyrrhizae should not be administered for prolonged use with thiazide and loop diuretics or cardiac glycosides (*29*). Because it reduces sodium and water excretion, the effectiveness of drugs used in the treatment of hypertension may be reduced. Radix Glycyrrhizae should not be administered in conjunction with spironolactone or amiloride (*52*).

Carcinogenesis, mutagenesis, impairment of fertility

Radix Glycyrrhizae is not mutagenic *in vitro* (*53–55*).

Pregnancy: teratogenic effects

The drug is not teratogenic in animal models (*56*).

Pregnancy: non-teratogenic effects

The safety of Radix Glycyrrhizae preparations during pregnancy has not been established. As a precautionary measure the drug should not be used during pregnancy.

Nursing mothers

The safety of Radix Glycyrrhizae preparations during lactation has not been established. As a precautionary measure the drug should not be used during lactation except on medical advice.

Paediatric use

The safety and effectiveness of the drug in children have not been established.

Other precautions

No information available about drug and laboratory test interactions.

Adverse reactions

No adverse reactions have been associated with the drug when used within the recommended dosage and treatment period.

Prolonged use (>6 weeks) of excessive doses (>50 g/day) can lead to pseudoaldosteronism, which includes potassium depletion, sodium retention, oedema, hypertension, and weight gain (*9*, *57*, *58*). In rare cases, myoglobinuria and myopathy can occur (*59*).

Posology

Unless otherwise prescribed, average daily dose of crude plant material, 5–15 g, corresponding to 200–800 mg of glycyrrhizin. Doses of other preparations should be calculated accordingly (*29*). Radix Glycyrrhizae should not be used for longer than 4–6 weeks without medical advice.

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Radix Paeoniae

Definition

Radix Paeoniae is the dried root of *Paeonia lactiflora* Pallas (Paeonaceae) (*1*, *2*).[1]

Synonyms

Paeonia albiflora Pallas., *P. edulis* Salisb., *P. officinalis* Thunb. (*5*, *6*).

Selected vernacular names

Báisháo, bo-báisháo, chuan-báisháo, hang-báisháo, mu-shaoyao, mudan, paeoniae alba, paeony, pai shao yao, pe-shou, peony, peony root, Pfingstrose, shakuyaku, shaoyao, syakuyaku, white peony, white-flowered peony (*2*, *4*, *6–8*).

Description

Paeonia lactiflora Pallas is a perennial herb, 50–80 cm high, with a stout branched root. Leaves alternate and biternately compound, the ultimate segments red-veined, oblong-elliptical. The leaflets are narrow-ovate or elliptical, 8–12 cm long and 2–4 cm wide. The petioles are 6–10 cm long. Flowers large (5–10 cm in diameter), solitary, and red, white, or purple. Sepals 4, herbaceous, persistent. Petals 5–10, larger than sepals. Stamens numerous and anthers yellow; carpels 3–5, many-seeded. Fruit, 3–5 coriaceous few-seeded follicles. Seeds large, subglobose; testa thick (*4*, *6*).

Plant material of interest: dried root

General appearance

Radix Paeoniae is cylindrical, straight or slightly curved, two ends truncate, 5–20 cm long and 1–2.5 cm in diameter; externally light greyish brown to reddish brown, glossy or with longitudinal wrinkles, rootlet scars and occasional remains of brown cork, and with laterally elongated lenticels; texture compact, easily broken, fracture relatively even, internally whitish or pale brownish red. Cambium ring distinct and rays radial (*1*, *2*).

[1] *Paeoniae veitchii* is described in the monograph "Radix Paeoniae Rubra" in the Chinese pharmacopoeia (*2*). Moutan Cortex, the root bark of *Paeonia moutan* Sims. (= *P. suffruticosa* Andr.) is also used in traditional medicine (*3–5*), and is listed as "Moutan Bark" in the Japanese pharmacopoeia (*1*).

Organoleptic properties

Odour, slight; taste, slightly sweet at first, followed by a sour or astringent taste and a slight bitterness (*1*, *2*).

Microscopic characteristics

Literature description not available; to be established in accordance with national requirements.

Powdered plant material

Light greyish brown powder; masses of gelatinized starch granules fairly abundant, 5–25 μm in diameter; clusters of calcium oxalate 11–35 μm in diameter, packed in parenchyma cells in rows or singly; bordered, pitted, or reticulate vessels 20–65 μm in diameter, walls thickened and slightly lignified (*1*, *2*).

Geographical distribution

China, India, and Japan (*6*).

General identity tests

Macroscopic, microscopic, and microchemical examinations; thin-layer chromatographic analysis for the presence of the monoterpene glycoside paeoniflorin (*1*, *2*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Paeoniae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*9–11*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 6.5% (*1*, *2*).

Acid-insoluble ash

Not more than 0.5% (*1*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Paeoniae is not more

than 0.05 mg/kg (*11*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*9*) and guidelines for predicting dietary intake of pesticide residues (*12*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*9*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*9*).

Other purity tests

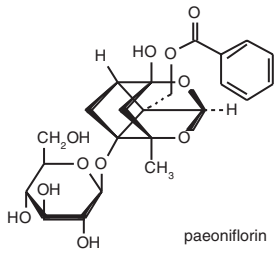
Alcohol-soluble extractive, chemical, foreign organic matter, moisture and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 2.0% of paeoniflorin (*1*, *2*), assayed by a combination of thin-layer chromatographic–spectrophotometric methods (*2*) or by high-performance liquid chromatography (*1*).

Major chemical constituents

Paeoniflorin, a monoterpene glycoside that is the major active constituent (*5*, *13*), is present in the range of 0.05–6.01% (*14*, *15*).



paeoniflorin

Dosage forms

Crude plant material, powder, and decoction. Store in a ventilated dry environment protected from light (*2*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As an analgesic, anti-inflammatory and antispasmodic drug in the treatment of amenorrhoea, dysmenorrhoea, and pain in the chest and abdomen (*2*). Radix Paeoniae is also used to treat dementia, headache, vertigo, spasm of the calf muscles (*2*, *4*, *5*), liver disease, and allergies, and as an anticoagulant (*8*, *13*).

Uses described in folk medicine, not supported by experimental or clinical data

The treatment of atopic eczema, boils, and sores (*5*); to reduce fevers, induce sterility, and treat burns (*8*).

Pharmacology

Experimental pharmacology

The primary pharmacological effects of Radix Paeoniae are antispasmodic, anti-inflammatory, and analgesic. A decoction of the drug had antispasmodic effects on the ileum and uterus when administered orally to mice, rabbits, and guinea-pigs (*13*). Similar effects were observed with a methanol extract in rat uterus (*16*), but an ethanol extract had uterine stimulant activity in rabbits (*17*). Radix Paeoniae extracts tested *in vitro* relaxed smooth muscles in both rat stomach and uterine assays (*13*).

Intragastric administration of a hot-water extract of Radix Paeoniae to rats inhibited inflammation in adjuvant-induced arthritis (*18*) and carrageenin-induced paw oedema (*19*). The major active constituent of the drug, paeoniflorin, a monoterpenoid glycoside, has sedative, analgesic, antipyretic, anti-inflammatory and vasodilatory effects *in vivo*. Hexobarbital-induced hypnosis was potentiated and acetic acid-induced writhing was inhibited in mice after intragastric administration of paeoniflorin (*20*, *21*).

Intragastric administration of hot-water or ethanol extracts of Radix Paeoniae to rats inhibited ADP-, arachidonic acid- and collagen-induced platelet aggregation, as well as endotoxin-induced disseminated intravascular coagulation (*22–24*). Similar effects were observed in rabbits and mice after intraperitoneal administration of the drug (*25*). When tested by the standard fibrin plate method, ethanol and hot-water extracts of the drug had antifibrinolytic activity *in vitro* (*26*). Paeoniflorin had anticoagulant activity both *in vitro* (*24*), and *in vivo* (in mice) (*27*).

Intragastric administration of extracts of Radix Paeoniae protected the liver against carbon tetrachloride-induced hepatotoxicity in mice and rats (*28*).

Oral administration of water extracts of Radix Paeoniae or its major con-

stituent, paeoniflorin, attenuated the scopolamine-induced impairment of radial maze performance in rats (*29*, *30*). Paeoniflorin prevented the scopolamine-induced decrease in acetylcholine content in the striatum, but not in the hippocampus or cortex (*30*). Oral administration of paeoniflorin further attenuated learning impairment of aged rats in operant brightness discrimination tasks (*31*). The results of this study suggest that further research to explore the therapeutic potential of paeoniflorin in cognitive disorders such as senile dementia may be promising (*31*).

Contraindications

Reports of traditional use indicate that Radix Paeoniae may have abortifacient activity; therefore, the use of Radix Paeoniae in pregnancy is contraindicated (*32*).

Warnings

No information available.

Precautions

Drug interactions

Radix Paeoniae should not be combined with *Fritillaria verticillata*, *Cuscuta japonica*, and *Rheum officinale* (*7*).

Carcinogenesis, mutagenesis, impairment of fertility

Hot-water or methanol extracts of Radix Paeoniae are not mutagenic *in vitro* (*33*, *34*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Excretion of the drug into breast milk and its effects on the newborn have not been established; therefore, use of the drug during lactation is not recommended.

Paediatric use

No information available; therefore, use of Radix Paeoniae in children is not recommended.

Other precautions

No information available about general precautions, drug and laboratory test interactions, or teratogenic effects on pregnancy.

Adverse reactions

No information available.

Posology

Maximum daily oral dose of crude plant material, 6–15 g (*2*), standardized for paeoniflorin.

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Semen Plantaginis

Definition

Semen Plantaginis is the dried, ripe seed of *Plantago afra* L., *P. indica* L., *P. ovata* Forsk., or *P. asiatica L.* (Plantaginaceae) (*1–4*).

Synonyms

Plantago afra L.

P. psyllium L. (*2*).

Plantago asiatica

None.

Plantago indica L.

P. arenaria Waldstein et Kitaibel, *P. ramosa* Asch. (*1*, *2*, *5*).

Plantago ovata Forsk.

P. ispaghula Roxb. (*4*).

Selected vernacular names

Psyllium seed, plantain seed, flea seed, Flohsamen, semences de psyllium (*6*).

P. afra L.

Flohsamen, Spanish psyllium (*6*).

P. asiatica

Shazen-shi, Che-qian-zi.

P. indica L.

Flashsamen, fleavort plantago, French psyllium, Spanish psyllium seed, whorled plantago (*6*).

P. ovata Forsk.

Ashwagolam, aspaghol, aspagol, bazarqutuna, blond psyllium, ch'-ch'ientzu, ghoda, grappicol, Indian plantago, Indische Psylli-samen, isabgol, isabgul,

isabgul gola, ispaghula, isphagol, vithai, issufgul, jiru, obeko, psyllium, plantain, spogel seeds (*1*, *6–9*).

Description

Plantago afra L.

An annual, erect, glandular-hairy caulescent herb, with an erect branching stem (0.2–0.4 m in height); it possesses whorls of flattened linear to linear-lanceolate leaves from the upper axils of which flowering stalks as long as the leaves arise. The stalks terminate in ovate-elliptical spikes up to 12 mm long. The upper bracts ovate-lanceolate up to 4 mm in length and somewhat similar in character to the lower bracts, but with chloroplastids fewer in the midrib of the proximal portion. The flowers are tetramerous with a calyx of 4 similar persistent, lanceolate sepals, each with green midrib and hyaline lamina, a hypocrateriform corolla of 4 gamopetalous hyaline petals inserted below the ovary, the tube surrounding the ovary and a portion of the filiform, hairy style, the limb with 4-lanceolate, acuminate lobes. The fruit is membranous, 2-celled and 2-seeded (*6*).

Plantago asiatica L.

Usually wrinkled and contracted leaf and spike, greyish green to dark yellow-green in colour; when soaked in water and smoothed out, the lamina is ovate or orbicular-ovate, 4–15 cm in length, 3–8 cm in width; apex acute, and base sharply narrowed; margin slightly wavy, with distinct parallel veins; glabrous or nearly glabrous; petiole is rather longer than the lamina, and its base is slightly expanded with thin-walled leaf-sheath; scape is 10–50 cm in length, one-third to one-half of the upper part forming the spike, with dense florets; the lower part of inflorescence often shows pyxidia; roots usually removed, but, if any, fine roots are closely packed (*6*).

Plantago indica L.

An annual caulescent herb attaining a height of 0.3–0.5 m with an erect or diffuse, hairy, frequently branched stem with whorls of linear to filiform leaves, from the axils of the upper ones of which spring peduncles, which are longer than the leaves and more or less umbellate. The lower bracts are transversely obovate below, lanceolate above, with a herbaceous midrib and hyaline margin, glandular hairy; the upper bracts broadly ovate with obtuse summits and also have herbaceous midribs and hyaline margins. The calyx is persistent, hairy, of 2 large spatulate anterior segments and 2 smaller, lateroposterior, lanceolate segments. The corolla is hypocrateriform of 4 petals, the limbs oblong with acute to mucronate summits; the tube of the corolla covering the pyxis and portions of the style. The pyxis is membranous, 2-celled, 2-seeded, and dehisces about or slightly below the middle (*6*).

Plantago ovata Forsk.

An annual, acaulescent herb, the stem of which is very ramified and bears linear leaves that are lanceolate, dentate, and pubescent. The flowers are white and grouped into cylindrical spikes. The sepals are characterized by a distinct midrib extending from the base to the summit; the petal lobes are oval with a mucronate summit. The seeds are oval and clearly carinate, measure 2–3 mm, and are a light grey-pink with a brown line running along their convex side (*6*, *7*).

Plant material of interest: seeds

General appearance

Plantago afra L.

Hemianatropous, silky to the touch; ovate to ovate-elongate, larger at one end than the other; concavo-convex; light to moderate brown, dark brown along the margin, very glossy. Length 1.3–2.7 mm, rarely up to 3 mm, and width 0.6–1.1 mm; the convex dorsal surface somewhat transparent, exhibiting a longitudinal brown area extending nearly the length of the seed and representing the embryo lying beneath the seed coat, and a transverse groove nearer the broader than the narrower end and over the point of union of the hypocotyl and cotyledons; the concave ventral surface with a deep excavation, in the centre of the base of which is an oval yellowish white hilum (*1*, *6*).

Plantago asiatica L.

Flattened ellipsoidal seed, 2–2.25 mm in length, 0.7–1 mm in width, 0.3–0.5 mm in thickness; externally brown to yellow-brown and lustrous. Under a magnifying glass, the surface of the seed is practically smooth; the dorsal side protrudes like a bow and the ventral side is somewhat dented; micropyle and raphe not observable. A hundred seeds weigh about 0.05 g (*3*).

Plantago indica L.

Ovate-oblong to elliptical; dark brown to maroon, often dull, rough and reticulate, 1.6–3.0 mm in length and 1.0–1.5 mm in width; concavo-convex, the dorsal surface has a longitudinal light brown area extending lengthwise along the centre and beneath the seed coat and has a median transverse groove, dent, or fissure; the ventral surface with a deep concavity, the edge of which is somewhat flattened and frequently forms a sharp indented angle with the base of the cavity, the latter showing a pale brown to occasionally whitish oval hilum (*1*, *6*).

Plantago ovata Forsk.

Boat-shaped with ovate outline, pinkish grey to brown in colour along the margin with opaque reticulate surface, 2–2.3 mm long, 1–1.5 mm wide and

1 mm thick, usually with central reddish brown oval patch extending about a third of the length of the seed. The convex dorsal surface has a longitudinal brown area extending nearly along the length of the seed that represents the position of the embryo lying beneath the seed-coat, and a transverse groove nearer to the broader than to the narrower extremity and over the points of union of the hypocotyl and cotyledons. The ventral surface shows a deep brown furrow that does not reach to either end of the seeds, in the centre of which is an oval yellowish white hilum, from which extends to the chalazal end a slightly elevated dark brown raphe. The seed is albuminous with oily endosperm; the embryo is straight, formed of two large plano-convex cotyledons and a small radicle in the narrow end and directed towards the micropyle. The seed is mucilaginous and upon soaking in water, the seed-coat swells and the seed becomes enveloped with a colourless mucilage. The weight of 100 seeds is about 0.1 g. A longitudinal cut, perpendicular to the ventral surface and passing through the hilum, shows a thin dark brown testa within which is a narrow endosperm surrounding a large oval lanceolate cotyledon and large pyramidal radicle directed towards the micropyle (*1*, *4*, *6*).

Organoleptic properties

Odourless with mucilage-like taste.

Microscopic characteristics

Plantago afra L.

The transverse sections of the seed cut through the central region possess a reniform outline and present for examination a spermoderm, endosperm, and embryo. The spermoderm shows an outer epidermis of mucilaginous epidermal cells with more or less obliterated walls in glycerine mounts; the radial and inner walls swell and disintegrate to form a clear mucilage upon irrigation of the mount with water; and a pigment layer with brown amorphous content. The endosperm composed of irregular-shaped, thick-walled cells with walls of reserve cellulose. The outer layer of this region consists of palisade cells 15–40 μm in height. Aleurone grains and fixed oils are found in the endosperm cells (*5*).

Plantago asiatica L.

Transverse section reveals a seed-coat consisting of three layers of epidermis composed of cells containing mucilage, a vegetative layer, and a pigment layer of approximately equidiameter cells; in the interior, endosperm thicker than seed-coat, enclosing 2 cotyledons (*6*).

Plantago indica L.

The transverse section of the seed shows a similar structure to that described above for *P. afra*, but the palisade cells of the endosperm are up to 52 μm in height (*6*).

***P. ovata* Forsk.**

The transverse cut through the central region possesses a reniform or a concave-convex outline and shows a testa, an endosperm, and 2 plano-convex cotyledons. Each cotyledon shows aleurone strands. On the convex surface a small raphe. The testa formed of one integument showing outer epidermis consisting of polygonal tabular cells with straight thin anticlinal walls covered with smooth cuticle. They are 52–68 μm long, 30–52 μm wide and 27–32 μm thick. The middle (nutrient) layer is formed of collapsed thin cellulosic parenchyma, usually more than one layer, about 5 or 6 rows. The inner epidermis consists of polygonal cells with straight thin anticlinal walls, containing reddish brown contents; they are 16–38 μm long, and 11–20 μm wide and 2–3 μm thick. The endosperm is formed of irregularly shaped thick cellulosic parenchyma showing an epidermis which is palisade-like, cells containing aleurone grains without inclusion, and fixed oil. The embryo formed of thin-walled cellulosic parenchyma containing fixed oil and aleurone grains. Each cotyledon shows 3 pleurone strands (*4*).

Powdered plant material

The most commonly used *P. ovata* powder is greyish brown showing glossy particles, colourless and with mucilage-like taste, characterized by fragments of epidermis formed of thin-walled polygonal cells with smooth cuticle and containing mucilage in the outer tangential and anticlinal walls, staining red with ruthenium red and blue with methylene blue; fragments of the pigment layer which is formed of polygonal cells with thin straight anticlinal walls with brown content traversed by collapsed colourless parenchyma; abundant fragments of endosperm with aleurone grains which are free of content and fixed oil; fragments of embryo tissues showing thin-walled parenchyma containing fixed oil and aleurone grains; few fragments showing spiral vessels attaining 11–15 μm width and few fibres which are elongated with thin pitted walls and pointed ends attaining 80–180 μm in length and 8–12 μm in width (*4*).

Geographical distribution

P. afra and *P. indica*, west Mediterranean countries (*6*); *P. asiatica,* Japan (*3*). *P. ovata*, Asia and the Mediterranean countries; the plant is cultivated extensively in India and Pakistan and adapts to western Europe and subtropical regions (*4*, *6*, *8–10*).

General identity tests

Macroscopic and microscopic examination (*1–4*); determining the swelling index (*1–4*); and test for reducing sugars (*3*, *4*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Semen Plantaginis products should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). Preparations for internal use: aerobic bacteria—not more than 10^5/g; fungi—not more than 10^4/g; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g; *Escherichia coli*—0/g.

Chemical

Swelling index of *P. afra* and *P. ovata*, not less than 10 (*2*); of *P. indica*, not less than 8 (*1*); of *P. asiatica*, to be established in accordance with national requirements.

Foreign organic matter

Not more than 0.5% (*1*).

Total ash

Not more than 4.0% (*1*).

Acid-insoluble ash

Not more than 1.0% (*1*).

Moisture

Not more than 14% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Semen Plantaginis is not more than 0.05 mg/kg (*2*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*13*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

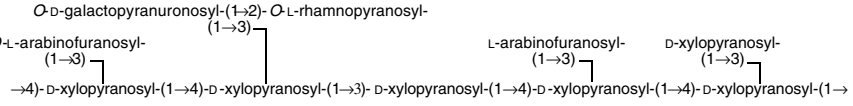
Tests for water-soluble extractive to be established in accordance with national requirements.

Chemical assays

Mucilage (10–30%) (*14*). *Plantago* products can be assayed for their fibre content by the method described by the Association of Official Analytical Chemists (*14*).

Major chemical constituents

Plantago seeds contain 10–30% mucilaginous hydrocolloid, which is localized in the outer seed-coat (husk) and is the major, active principle. The mucilage is composed of a soluble polysaccharide fraction containing mainly arabinoxylans (85%). The polymer backbone is a xylan with 1 → 3 and 1 → 4 linkages, with no apparent regularity in their distribution. The monosaccharides in this main chain are substituted on C-2 or C-3 by L-arabinose, D-xylose, and α-D-galacturonyl-(1 → 2)-L-rhamnose. In addition, secondary metabolites in the seed include sterols, triterpenes, and aucubin glycosides (*4–7*, *15*).



Dosage forms

Seeds, powder, and granules. Store in well-closed containers, in a cool dry place, protected from light (*1–4*).

Medicinal uses

Uses supported by clinical data

As a bulk-forming laxative used to restore and maintain regularity (*2*, *4*, *16–20*). Semen Plantaginis is indicated in the treatment of chronic constipation, temporary constipation due to illness or pregnancy, irritable bowel syndrome, constipation related to duodenal ulcer or diverticulitis (*17–22*). It is also used to soften the stools of those with haemorrhoids, or after anorectal surgery (*16*, *17*).

Uses described in pharmacopoeias and in traditional systems of medicine

While Semen Plantaginis is primarily used in the treatment of constipation, it has also been used effectively in the short-term symptomatic treatment of diarrhoea of various etiologies (*23*, *24*).

Uses described in folk medicine, not supported by experimental or clinical data

Other medical uses claimed for Semen Plantaginis include use as an expectorant and antitussive, an antibacterial agent, and a diuretic and in the treatment of rheumatic and gouty afflictions, glandular swelling, and bronchitis (*8*).

Pharmacology

Clinical pharmacology

Constipation

Semen Plantaginis increases the volume of the faeces by absorbing water in the gastrointestinal tract, which stimulates peristalsis (*25*, *26*). The intraluminal pressure is decreased, colon transit is increased, and the frequency of defecation is increased (*15*, *16*, *25*).

When mixed with water, the therapeutic efficacy of the drug is due to the swelling of the mucilaginous seed coat which gives bulk and lubrication (*7*). Semen Plantaginis increases stool weight and water content owing to the water-bound fibre residue and an increased faecal bacterial mass. Clinical studies have demonstrated that ingestion of 18 g of Semen Plantaginis significantly increases faecal fresh and dry weights as compared with weights obtained with placebo (*15*).

Antidiarrhoeal activity

The antidiarrhoeal effects of Semen Plantaginis have been extensively investigated in patients with acute and chronic diarrhoea (*23*, *24*). An increase in the viscosity of the intestinal contents due to the binding of fluid and an increased colonic transit time (decreased frequency of defecation) were observed in patients treated with the drug (*23*, *24*).

Contraindications

Known hypersensitivity or allergy to the plant; faecal impaction or intestinal obstruction; diabetes mellitus where insulin adjustment is difficult (*27*).

Warnings

Semen Plantaginis products should always be taken with sufficient amounts of liquid, and at least half an hour after other medications to prevent delayed absorption of the latter. If bleeding or no response occurs after ingesting the drug, or if abdominal pain occurs 48 hours after treatment, treatment should be stopped and medical advice sought. If diarrhoea persists longer than 3 or 4 days, medical attention should be sought (*28*).

To prevent the generation of airborne dust, users should spoon the product from the container directly into a drinking glass and then add liquid (*28*). To minimize the potential for allergic reaction, health professionals who frequently dispense powdered Semen Plantaginis should avoid inhaling airborne dust while handling these products.

Precautions

General

Semen Plantaginis should be taken with adequate volumes of fluid. It should never be taken orally as the dried powder, because of the possibility of bowel obstruction. In patients who are confined to bed or do little physical exercise, a medical examination may be necessary prior to treatment with the drug.

Drug interactions

Bulking agents have been reported to diminish the absorption of some minerals (calcium, magnesium, copper, and zinc), vitamin B_{12}, cardiac glycosides, and coumarin derivatives (*29–31*). The co-administration of Semen Plantaginis with lithium salts has been reported to reduce the plasma concentrations of the lithium salts and may inhibit their absorption from the gastrointestinal tract (*32*). Semen Plantaginis has also been reported to decrease both the rate and extent of carbamazepine absorption, inducing subclinical levels of the drug (*33*). Therefore, ingestion of lithium salts or carbamazepine and Semen Plantaginis should be separated in time as far as possible (*33*). Individual monitoring of the plasma levels of the drug in patients taking Semen Plantaginis products is also recommended. Insulin-dependent diabetic people may require less insulin (*27*).

Other precautions

No information available concerning carcinogenesis, mutagenesis, impairment of fertility; drug and laboratory test interactions; nursing mothers, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

Sudden increases in dietary fibre may cause temporary gas and bloating. These side-effects may be reduced by gradually increasing fibre intake, starting at one dose per day and gradually increasing to three doses per day (*28*). Occasional flatulence and bloating may be reduced by decreasing the amount of Semen Plantaginis taken for a few days (*28*).

Allergic reactions to *Plantago* products in response to ingestion or inhalation have been reported, especially after previous occupational exposure to these products (*34–36*). These reactions range from urticarial rashes to anaphylactic reactions (rare). One case of fatal bronchospasm has been reported in a *Plantago*-sensitive patient with asthma (*34*).

Posology

The suggested average dose is 7.5 g dissolved in 240 ml water or juice taken orally 1–3 times daily depending on the individual response. The recommended dose for children aged 6–12 years is one-half the adult dose. For children under 6 years, a physician should be consulted. An additional glass of liquid is recommended after ingestion of the drug and generally provides an optimal response. Continued use for 2 or 3 days is needed for maximum laxative benefit.

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Radix Platycodi

Definition

Radix Platycodi is the root of *Platycodon grandiflorum* (Jacq.) A. DC. (Campanulaceae) (*1*, *2*).

Synonyms

Platycodon chinensis Lindl, *P. autumnalis* Decne., *P. sinensis* Lem., *P. stellatum*, *Campanula grandiflora* Jacq., *Campanula glauca* Thunb., *Campanula gentianoides* Lam. (*3*, *4*).

Selected vernacular names

Balloon-flower, chieh keng, Chinese bell flower, gil gyeong, Japanese bell-flower, jiegeng, jieseng, kikiyou, kikyo, kikyokon, kikyou, platycodon radix (*3–8*).

Description

Perennial herb wholly glabrous, slightly glaucescent; root white, fleshy, radish-shaped, finger-thick, with abundant milky juice; stems ascending from base or straight, simple, 40–50 cm, herbaceous, glabrous or smooth, longitudinally striate in lower part; radical leaves alternate or sometimes nearly opposite, arranged along the lower half of stem or even higher, ovate-lanceolate, sessile, tapering at base, 2.5–3.4 cm long, 2–3 cm wide, rather large-toothed, pale beneath, glaucescent, upper leaves reduced. Flowers usually 1, sometimes 2, large, lengthily pedunculate, broadly campanulate or deeply saucer-shaped; calyx in 5 segments; corolla 5-lobed, violet-blue, 4 cm long; stamens 5; ovary many-celled. Fruit an ovoid capsule dehiscent at the top; seeds ovoid, compressed, obtuse, first violet then brown; albumen fleshy (*3*, *9*).

Plant material of interest: dried root

General appearance

The root is irregular, somewhat thin and long fusiform, tapering, conical, often branched; externally greyish brown, light brown, or white; main root 10–15 cm in length, 1–3 cm in diameter at the upper end, with dented scars of removed stems, fine lateral wrinkles and longitudinal furrows, and slightly constricted;

the remaining part of the root, except the crown, covered with coarse longitudinal wrinkles, lateral furrows and lenticel-like lateral lines; hard in texture, but brittle; fractured surface not fibrous, often with cracks. Under a magnifying glass, a transverse section reveals cambium and its neighbourhood often brown in colour; cortex slightly thinner than xylem, almost white and with scattered cracks; xylem white to light brown and the tissue slightly denser than cortex (*2*).

Organoleptic properties

Odour, odourless; taste, tasteless at first, later bittersweet and pungent; colour, greyish brown (*1*, *2*).

Microscopic characteristics

In transverse section of whole peeled root, cork cells occasionally remain; unpeeled roots show cork layers. Cork cells contain calcium oxalate prisms. Cortex narrow, often with clefts. Phloem scattered with laticiferous tube groups, walls somewhat thickened; contains yellowish brown granules. Cambium in a ring. Xylem vessels singly scattered or aggregated in groups arranged radially. Parenchymatous cells contain inulin (*1*).

Powdered plant material

Light greyish yellow to light greyish brown powder containing numerous fragments of colourless parenchyma cells; fragments of reticulate vessels and scalariform vessels; fragments of sieve tubes and lactiferous tubes; fragments of cork layer are sometimes observed. Starch grains are not usually observed, but very rarely simple grains are present, ellipsoid to irregular spheroid, 12–25 μm in diameter (*2*).

Geographical distribution

Northern Asia, China, the Democratic People's Republic of Korea, Japan, the Republic of Korea, the Russian Federation (east Siberia) (*3*, *7*, *9*).

General identity tests

Macroscopic and microscopic examinations; microchemical tests for saponins (*1*, *2*), thin-layer chromatographic analysis for characteristic saponin profile (*10*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Platycodi should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not

more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 4.0% (*2*).

Acid-insoluble ash

Not more than 1.0% (*2*).

Alcohol-soluble extractive

Not less than 25% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Radix Platycodi is not more than 0.05 mg/kg (*13*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*14*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

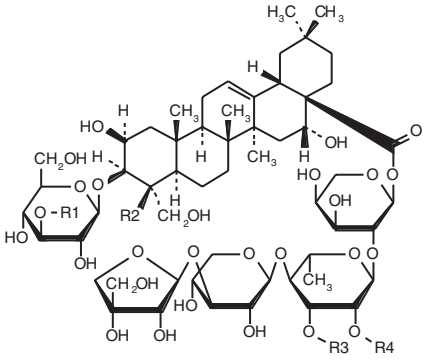
Chemical, foreign organic matter, moisture, and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Triterpene saponins, not less than 2% (*6*). Saponin content of the root can be evaluated by thin-layer chromatography–densitometry (*10*).

Major chemical constituents

The major chemical constituents of Radix Platycodi root are triterpene saponins based on the sapogenins platycodigenin and polygalacic acid; examples are platycodins A–I and polygalacins D and D_2 (*6*, *15*).



	R1	R2	R3	R4
platycodin A	H	CH_2OH	H	$CO\text{-}CH_3$
platycodin C	H	CH_2OH	$CO\text{-}CH_3$	H
platycodin D	H	CH_2OH	H	H
platycodin D_2	glc *	CH_2OH	H	H
polygalacin D	H	CH_3	H	H
polygalacin D_2	glc *	CH_3	H	H

* glc = β-D-glucopyranosyl

Dosage forms

Dried roots, extracts, and other preparations.

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As an expectorant and antitussive (*1, 3–5*) used to treat coughs, colds, upper respiratory infections, sore throats, tonsillitis, and chest congestion (*1*, *7*). In Chinese traditional medicine, Radix Platycodi has been used to treat cough with sputum, tonsillitis, pertussis, and asthma (*16*). Also used to treat stomatitis, peptic ulcers, and chronic inflammatory diseases (*17*, *18*).

Uses described in folk medicine, not supported by experimental or clinical data

Other medical uses for Radix Platycodi include the treatment of viral infections and high blood pressure (*6*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

The anti-inflammatory activity of Radix Platycodi has been attributed to the platycodins (*17*, *19*, *20*). *In vivo* studies have shown that intragastric administration of the drug antagonized carrageenin- and acetic acid-induced swelling of rat paws, and oral administration markedly inhibited cotton pledget-induced granulation in rats (*21*). Platycodins also effectively inhibited adjuvant-induced arthritis in rats (*22*). Researchers investigating some Japanese Kampo medicines

concluded that Radix Platycodi was at least partly responsible for the anti-inflammatory activity of these preparations (*17*).

Expectorant and antitussive activity

Radix Platycodi has both antitussive and expectorant activities (*18*, *20*). The expectorant effects include the promotion of salivary and bronchial secretions (*6*). Oral administration of a decoction of the drug (1 g/kg) to anaesthetized dogs increased mucus secretions in the respiratory tract with a potency similar to that of ammonium chloride (*23*). A similar response was observed in cats (*24*). The platycodins are believed to be the active components. Oral doses of platycodins irritated the pharyngeal and gastric mucosa, increasing mucosal secretions in the respiratory tract and diluting sputum for easy expectoration (*25*).

In vivo studies have demonstrated the effectiveness of platycodins as an antitussive drug. When administered to guinea-pigs, platycodins reduced the frequency of coughing; the median effective dose was 6.4 mg/kg given intraperitoneally (*5*, *26*). A 20% decoction of Radix Platycodi was also effective in treating coughing induced by ammonia in mice (*6*).

Antipeptic ulcer activity

Platycodins have been reported to inhibit gastric secretion and prevent peptic ulcer in rats (*5*). A dose of 100 mg/kg inhibited gastric secretion in rats induced by ligation of the pylorus and stress ulceration (*18*).

Antihypercholesterolaemic and antihyperlipidaemic activity

An effect of Radix Platycodi on serum and liver lipid concentrations has been demonstrated. Rats with diet-induced hyperlipidaemia were fed diets containing 5% and 10% Radix Platycodi. The rats fed with the 5% diet had significantly lower concentrations of total cholesterol and triglycerides in serum and of liver lipids than did controls (*27*).

Toxicity

The median lethal dose of a decoction of Radix Platycodi given orally was 24 g/kg in mice (*5*). The median lethal doses of platycodins in mice and rats were 420 and 800 mg/kg (oral), or 22.3 and 14.1 mg/kg (intraperitoneal), respectively (*5*). Crude platycodins have been reported to have sedative side-effects in mice, such as inhibition of movement and a decrease in respiration after both intraperitoneal and oral administration (*18*). These side-effects were less pronounced after oral administration, suggesting that platycodins are poorly absorbed through the gastrointestinal tract (*18*).

Crude platycodins have a highly haemolytic effect in mice, of which the haemolytic index is 1.2 times that of a commercial reagent-grade saponin used as a reference (*5*, *18*). Radix Platycodi preparations should therefore be given

only orally, after which the drug loses its haemolytic effect owing to decomposition in the alimentary tract (*18*).

Clinical pharmacology

Crude powdered drug or decoctions of Radix Platycodi have been used to treat the symptoms of lung abscesses, lobar pneumonia, and pharyngitis with reported success (*5*). However, the details of these clinical studies were not available.

Contraindications

No information available.

Warnings

Playtcodon extracts have a very pronounced haemolytic effect, and therefore the drug should not be administered by injection (*5*).

Precautions

General

Radix Platycodi reportedly depresses central nervous system (CNS) activity (*5*). Patients should avoid using alcohol or other CNS depressants in conjunction with this drug. Patients should be cautioned that the combination of the drug and alcohol may impair their ability to drive a motor vehicle or operate hazardous machinery.

Drug interactions

Because of the CNS depressant activity (*5*), Radix Platycodi may act synergistically with other CNS depressants such as alcohol, tranquillizers, and sleeping medications. Radix Platycodon is also reported to be incompatible with *Gentiana scabra* and *Bletilla hyacinthina* (*5*).

Carcinogenesis, mutagenesis, impairment of fertility

To date, no genotoxic effects have been reported. *Platycodon* root extracts were not mutagenic in the *Bacillus subtilis rec*-assay or the *Salmonella*/microsome reversion assay (*28*). Nor were they mutagenic in the SOS chromotest (*E. coli* PQ37) and in the SOS *umu* test (*S. typhimurium* TA 1535/pSK 1002) (*29*).

Pregnancy: teratogenic effects

Platycodon extracts are not teratogenic *in vivo* (*30*).

Pregnancy: non-teratogenic effects

No data available; therefore Radix Platycodi should not be administered during pregnancy.

Nursing mothers

Excretion of the drug into breast milk and its effects on the newborn infant have not been established; therefore the use of the drug during lactation is not recommended.

Other precautions

No information available on drug and laboratory test interactions or on paediatric use.

Adverse reactions

No information available.

Posology

The usual dose range is 2–9 g daily (*1*, *3*, *6*).

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Radix Rauwolfiae

Definition

Radix Rauwolfiae is the dried root of *Rauvolfia serpentina* (L.) Benth. ex Kurz (Apocynaceae) (*1–4*).

Synonyms

Ophioxylon obversum Miq., *O. sautiferum* Salisb., *O. serpentinum* L., *Rauvolfia obversa* (Miq.) Baill., *R. trifoliata* (Gaertn.) Baill. (*3–5*).

Selected vernacular names

Most commonly called "rauwolfia". Acawerya, aika-wairey, akar-tikos, arsol, bhudra, bongmaiza, chandmaruwa, chandra, chandrika, chotachand, chota-chard, chundrika, chundrooshoora, churmuhuntree, chuvannayilpuri, covanamilpori, covannamipori, dhanbarua, dhannerna, dogrikme, eiya-kunda, ekaweriya, garudpathal, hadki, harkai, harkaya, ichneumon plant, Indian snake-root, indojaboku, karai, karavi, karuvee, makeshwar chadrika, makeshwar churna, matavi-aloos, nogliever, nundunee, pagla-ka-dawa, palalganni, patala-agandhi, poelé pandak, poeleh pandak, pushoomehnunkarika, ra-yom, radix mungo, radix mustelae, raiz de mongo alba, rametul, ratekaweriya, rayom noi, rauvolfia, rauwalfia, rauwolfia, Rauwolfiawurzel, sanochado, sapasan, sarpagandha, sarpgandha, serpentina, sjouanna-amelpodi, snakeroot, sung, suvapaval-amepodi, talona, vasoopooshpa, vasura (*5–8*).

Description

Small, erect, glabrous shrub, 30–60 cm high. Leaves whorled, 7.5–17.5 cm long, lanceolate or oblanceolate, acute or acuminate, tapering gradually into the petiole, thin. Flowers white or pinkish; peduncles 5.0–7.5 cm long; pedicels and calyx red. Calyx lobes 2.5 mm long, lanceolate. Corolla about 1–1.3 cm long; tube slender; inflated slightly above middle; lobes much shorter than tube, obtuse. Drupes about 6 mm (diameter), single or didymous and more or less connate, purplish black when ripe (*1*).

Plant material of interest: root

General appearance

The root occurs as segments 5–15 cm in length and 3–20 mm in diameter, subcylindrical to tapering, tortuous or curved, rarely branched, occasionally bearing twisted rootlets, which are larger, more abundant, and more rigid and woody on the thicker parts of the roots. Externally light brown to greyish yellow to greyish brown, dull, rough or slightly wrinkled longitudinally, yet smooth to the touch, occasionally showing rootlet scars on the larger pieces, with some exfoliation of the bark in small areas that reveals the paler wood beneath. Bark separates easily from the wood on scraping. Fracture short but irregular, the longer pieces readily breaking with a snap, slightly fibrous marginally. The freshly fractured surfaces show a rather thin layer of greyish yellow bark, and the pale yellowish white wood constitutes about 80% of the radius. The smooth transverse surface of larger pieces shows a finely radiate stele with three or more clearly marked growth rings; a small knob-like protuberance is frequently noticeable in the centre. The wood is hard and of relatively low density (*1*).

Organoleptic properties

Root odour is indistinct, earthy, reminiscent of stored white potatoes, and the taste is bitter (*1*).

Microscopic characteristics

A transverse section of the root shows externally 2–8 alternating strata of cork cells, the strata with larger cells alternating with strata made up of markedly smaller cells. Each stratum composed of smaller cells includes 3–5 tangentially arranged cell layers. In cross-sectional view, the largest cells of the larger cell group measure 40–90 μm radially and up to 75 μm tangentially, while the cells of the smaller group measure 5–20 μm radially and up to 75 μm tangentially. The walls are thin and suberized. The secondary cortex consists of several rows of tangentially elongated to isodiametric parenchyma cells, most densely filled with starch grains; others (short latex cells) occur singly or in short series and contain brown resin masses. The secondary phloem is relatively narrow and is made up of phloem parenchyma (bearing starch grains and less commonly tabular to angular calcium oxalate crystals up to 20 μm in length; also, occasionally, with some brown resin masses in outer cells and phloem rays) interlaid with scattered sieve tissue and traversed by phloem rays 2–4 cells in width. Sclerenchyma cells are absent in root (a distinction from other *Rauvolfia* species). Cambium is indistinct, narrow, dark, and wavering. The secondary xylem represents the large bulk of the root and shows one or more prominent annual rings with a dense core of wood about 500 μm across at the centre. The xylem is composed of many wood wedges separated by xylem rays, and on closer examination reveals vessels in interrupted radial rows, much xylem paren-

chyma, many large-celled xylem rays, few wood fibres, and tracheids, all with lignified walls. The xylem fibres occur in both tangential and radial rows. The xylem rays are 1–12, occasionally up to 16 cells in width (*1*, *3*).

Powdered plant material

Powdered Radix Rauwolfiae is brownish to reddish grey. Numerous starch grains (simple, 2- to 3-compound, occasionally 4-compound) present; simple grains spheroid, ovate, plano- to angular-convex, or irregular; hilum simple, Y-shaped, stellate, or irregularly cleft; unaltered grains 6–34 μm in diameter; altered grains up to about 50 μm; large unaltered grains clearly show polarization cross; calcium oxalate prisms and cluster crystals scattered, about 10–15 μm in size; brown resin masses and yellowish granular secretion masses occur occasionally; isolated cork cells elongated, up to 90 μm in length; phelloderm and phloem parenchyma cells similar in appearance; vessels subcylindrical, up to 360 μm in length and about 20–57 μm in diameter, the vessel end walls oblique to transverse, generally with openings in the end walls, some vessels showing tyloses; tracheids pitted, with moderately thick, tapering, beaded walls, with relatively broad lumina, polygonal in cross-section; xylem parenchyma cells with moderately thick walls with simple circular pits, cells polygonal in cross-section, bearing much starch, sometimes with brown resin masses; xylem fibres with thick heavily lignified walls showing small transverse and oblique linear pits and pointed simple to bifurcate ends, measuring about 200–750 μm in length. No phloem fibres or sclereids are present in root (colourless non-lignified pericycle or primary phloem fibres, single or in small groups, may be present from rhizome or stem tissues) (*1*).

Geographical distribution

The plant is found growing wild in the sub-Himalayan tracts in India and is also found in Indonesia, Myanmar, and Thailand (*3*).

Overcollection of Radix Rauwolfiae in India has significantly diminished supply and since 1997 there has been an embargo on export of this drug from India. Reserpine is currently either extracted from the roots of *Rauvolfia vomitoria* of African origin or produced by total synthesis.

General identity tests

Macroscopic and microscopic examinations (*1*–*3*) and thin-layer chromatographic analysis for the presence of characteristic indole alkaloids (*2*, *3*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Rauwolfiae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*9*–*11*).

For preparation of decoction: aerobic bacteria—not more than 10^7/g; moulds and yeast—not more than 10^4/g; *Escherichia coli*—not more than 10^2/g; other enterobacteria—not more than 10^4/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g; moulds and yeast—not more than 10^3/g; *Escherichia coli*—not more than 10^1/g; other enterobacteria—not more than 10^3/g.

Foreign organic matter

Not more than 2.0% of stems, and not more than 3.0% of other foreign organic matter (*1*).

Total ash

Not more than 10% (*2*).

Acid-insoluble ash

Not more than 2.0% (*1*, *2*).

Moisture

Not more than 12% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Radix Rauwolfiae is not more than 0.05 mg/kg (*11*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*9*) and guidelines for predicting dietary intake of pesticide residues (*12*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*9*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*9*).

Other purity tests

Chemical, alcohol-soluble extractive and water-soluble extractive tests to be established in accordance with national requirements.

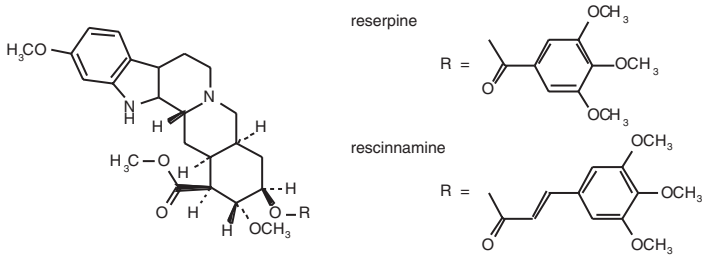
Chemical assays

Contains not less than 1% total alkaloids (*2*, *3*); and a minimum of 0.1% alkaloids of the reserpine–rescinnamine group (*3*).

Thin-layer chromatography to detect the presence of the reserpine–rescinnamine group of alkaloids (*2*, *3*, *13*). Quantitative analysis of total and reserpine–rescinnamine group of alkaloids can be performed by spectrophotometric analysis (*2*, *3*) or by high-performance liquid chromatography (*14*, *15*).

Major chemical constituents

Radix Rauwolfiae contains more than 60 indole alkaloids; the principal hypotensive alkaloids are identified as reserpine and rescinnamine (*1*, *6*).



Dosage forms

Crude drug and powder. Package in well-closed containers and store at 15–25 °C (*9*) in a dry place, secure against insect attack (*1*).

Medicinal uses

Uses supported by clinical data

The principal use today is in the treatment of mild essential hypertension (*16–22*). Treatment is usually administered in combination with a diuretic agent to support the drug's antihypertensive activity, and to prevent fluid retention which may develop if Radix Rauwolfiae is given alone (*18*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a tranquillizer for nervous and mental disorders (*4*, *5*).

Uses described in folk medicine, not supported by experimental or clinical data

As a tonic in states of asthenia, a cardiotonic and antipyretic; against snake and insect bites; and for constipation, liver diseases, flatulence, insomnia, and rheumatism (*8*).

Pharmacology

Experimental pharmacology

It is well accepted that the pharmacological effects of Radix Rauwolfiae are due to its alkaloids, especially the reserpine–rescinnamine group. The experimental pharmacology of reserpine and related compounds has been well documented (*5*, *16–18*, *23*). Powdered Radix Rauwolfiae, as well as various forms of extracts (ethanolic, dried), has been reported to lower the blood pressure of experimental animals (dogs or cats) by various routes of administration (*5*).

Clinical pharmacology

Radix Rauwolfiae and its major alkaloids probably lower high blood pressure by depleting tissue stores of catecholamines (epinephrine and norepinephrine) from peripheral sites. By contrast, their sedative and tranquillizing properties are thought to be related to depletion of catecholamines and serotonin (5-hydroxytryptamine) from the brain. Following absorption from the gastrointestinal tract the active alkaloids concentrate in tissues with high lipid content. They pass the blood–brain barrier and the placenta. Radix Rauwolfiae products are characterized by slow onset of action and sustained effect. Both the cardiovascular and central nervous system effects may persist following withdrawal of the drug. The active alkaloids are metabolized in the liver to inactive compounds that are excreted primarily in the urine. Unchanged alkaloids are excreted primarily in the faeces (*16*).

Contraindications

Radix Rauwolfiae products are contraindicated in patients who have previously demonstrated hypersensitivity to the plant or its alkaloids. They are also contraindicated in patients with a history of mental depression (especially those with suicidal tendencies) during or shortly after therapy with monoamine oxidase inhibitors; active peptic ulcer, sinus node disorders, ulcerative colitis; epilepsy; or decreased renal function; and in patients receiving electroconvulsive therapy (*16*, *18*).

Warnings

Radix Rauwolfiae products may cause mental depression (*24*). Recognition of depression may be difficult because this condition may often be disguised by somatic complaints (masked depression). The products should be discontinued at first signs of depression such as despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The use of Radix Rauwolfiae products may impair alertness and make it inadvisable to drive or operate heavy machinery (*16*, *18*).

Precautions

General

Because Radix Rauwolfiae preparations increase gastrointestinal motility and secretion, they should be used cautiously in persons with a history of peptic ulcer, ulcerative colitis, or gallstones where biliary colic may be precipitated. Persons on high doses should be observed carefully at regular intervals to detect possible reactivation of peptic ulcer (*16*).

Caution should be exercised when treating hypertensive patients with renal insufficiency since they adjust poorly to lowered blood-pressure levels (*16*).

Drug interactions

When administered concurrently, the following drugs may interact with or potentiate Radix Rauwolfiae and its alkaloids (*16*, *18*): alcohol or other central nervous system depressants, other antihypertensives or diuretics, digitalis glycosides or quinidine, levodopa, levomepromazine, monoamine oxidase inhibitors, sympathomimetics (direct-acting) and tricyclic antidepressants.

Concomitant use of Radix Rauwolfiae products and anaesthetics may provoke a fall in blood pressure (*4*, *17*, *25*) and add to the β-adrenoceptor–blocking activity of propranolol (*25*).

Drug and laboratory test interactions

Chronic administration of Radix Rauwolfiae preparations may increase serum prolactin levels and decrease excretion of urinary catecholamines and vanilmandelic acid. Therefore, any diagnostic tests performed for these determinations should be interpreted with caution (*16*).

Radix Rauwolfiae preparations slightly decrease absorbance readings obtained on urinary steroid colorimetric determinations (e.g. modified Glenn–Nelson technique or Holtorff Koch modification of Zimmermann reaction), and thus false low results may be reported (*16*).

Preoperative withdrawal of Radix Rauwolfiae products does not necessarily ensure circulatory stability during the procedure, and the anaesthetist must be informed of the patient's drug history (*4*, *17*, *25*).

Caution is indicated in elderly patients and also in those suffering from coronary and cerebral arteriosclerosis. Administration of products including Radix Rauwolfiae preparations at doses that might precipitate a sharp decrease in blood pressure should be avoided (*17*).

Carcinogenesis, mutagenesis, impairment of fertility

Animal carcinogenicity studies using reserpine at doses 50 times as high as the average human dose have been conducted with rats and mice. Carcinogenic effects associated with the administration of reserpine include an increased incidence of adrenal medullary phaeochromocytomas in male rats, unidentified carcinomas of the seminal vesicles in male mice, and mammary cancer in female mice; carcinogenic effects were not seen in female rats (*14*, *23*, *26*).

Bacteriological studies to determine mutagenicity using reserpine showed negative results (*16*). The extent of risk to humans is uncertain (*16*, *26–28*).

Pregnancy: teratogenic effects

Reserpine, the major active alkaloid in Radix Rauwolfiae, administered parenterally has been shown to be teratogenic in rats at doses up to 2 mg/kg and to have an embryocidal effect in guinea-pigs at 0.5 mg daily (*27*). There are no adequate and well-controlled studies in pregnant women.

Pregnancy: non-teratogenic effects

Increased respiratory secretions, nasal congestion, cyanosis, hypothermia, and anorexia have occurred in neonates of mothers treated with Radix Rauwolfiae (*16*, *28*, *29*). Therefore, the use of Radix Rauwolfiae is not recommended during pregnancy.

Nursing mothers

Rauwolfia alkaloids are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, use of Radix Rauwolfiae during lactation is not recommended.

Paediatric use

Safety and effectiveness in children have not been established (*16*).

Adverse reactions

The following adverse reactions have been observed, but there are insufficient data to support an estimate of their frequency. The reactions are usually reversible and disappear when the Radix Rauwolfiae preparations are discontinued (*16*, *18*).

Cardiovascular system: bradycardia, arrhythmias, particularly when used concurrently with digitalis or quinidine, angina-like symptoms. Water retention with oedema in persons with hypertensive vascular disease may occur rarely, but the condition generally clears with cessation of therapy, or the administration of a diuretic agent. Vasodilation produced by rauwolfia alkaloids may result in nasal congestion, flushing, a feeling of warmth, and conjunctival congestion.

Central nervous system: sensitization of the central nervous system manifested by optic atrophy, glaucoma, uveitis, deafness, and dull sensorium. Other reactions include depression, paradoxical anxiety, nightmares, nervousness, headache, dizziness, drowsiness. Large doses have produced parkinsonian syndrome, other extrapyramidal reactions, and convulsions.

Gastrointestinal system: hypersecretion and increased intestinal motility, diarrhoea, vomiting, nausea, anorexia, and dryness of mouth. Gastrointestinal bleeding has occurred in isolated cases.

Respiratory system: dyspnoea, epistaxis, nasal congestion.

Hypersensitivity: purpura, pruritus, rash.

Other: dysuria, muscular aches, weight gain, breast engorgement, pseudolactation, impotence or decreased libido, gynaecomastia.

Posology

Powder, 200 mg daily in divided doses for 1–3 weeks; maintenance 50–300 mg daily (*1*). Doses of other preparations should be calculated accordingly. Doses of Radix Rauwolfiae should be based on the recommended dosage of rauwolfia alkaloids, which must be adjusted according to the patient's requirements and tolerance in small increments at intervals of at least 10 days. Debilitated and geriatric patients may require lower dosages of rauwolfia alkaloids than do other adults (*18*). Rauwolfia alkaloids may be administered orally in a single daily dose or divided into two daily doses (*18*).

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Rhizoma Rhei

Definition

Rhizoma Rhei consists of the underground parts (rhizome and root) of *Rheum officinale* Baill., or *R. palmatum* L. (Polygonaceae) (*1–7*).[1]

Synonyms

None.

Selected vernacular names

Akar kalembak, Chinese rhubarb, chuòng diêp dai hoàng, dai hoàng, daioh, daiou, kot nam tao, rawind, Rhabarberwurzel, rhabarbarum, rhubarb, rhubard de Chine, rhubarb root, turkey rhubarb, ta-huang (*8–10*).

Description

Rheum species are perennial herbs resembling the common garden rhubarb except for their lower growth and shape of their leaf blades; the underground portion consists of a strong vertical rhizome with fleshy, spreading roots; the portion above ground consists of a number of long petioled leaves that arise from the rhizome in the spring, and flower shoots bearing elongated leafy panicles that are crowded with greenish white, white, to dark purple flowers; the lamina is cordate to somewhat orbicular, entire or coarsely dentate (*Rheum officinale*) or palmately lobed (*R. palmatum*). The fruit is an ovoid-oblong or orbicular achene bearing 3 broad membranous wings and the remains of the perianth at the base (*9*, *11*).

Plant material of interest: rhizomes and roots

General appearance

The appearance of the rhizomes and roots varies according to the plant's geographical origin (*12*). They occur on the market in subcylindrical, barrel-shaped, plano-convex or irregularly formed pieces, frequently showing a perfo-

[1] *Rheum tangutium* Max., *R. coreanum* Nakai, *R. palmatum* L., and *R. officinale* Baillow, or their interspecific hybrids, are also listed in the Japanese pharmacopoeia (*1*). *R. emodi* ("Indian rhubarb") is listed in the Indian pharmacopoeia (*7*).

ration, or in cubes or rectangular pieces, the last commonly known as "rhubarb fingers". They are hard and moderately heavy. The outer surfaces are smooth, longitudinally wrinkled or sunken, yellowish brown and mottled with alternating striae of greyish white parenchyma and brownish or reddish medullary rays, while here and there may be seen brown cork patches and branched scars, "star spots", of leaf trace fibrovascular bundles. The fracture is uneven and granular, the fractured surface pinkish brown. The smooth transverse surface of the rhizome exhibits a cambium line near the periphery traversed by radial lines that represent medullary rays that project for a short distance within it. The large area within this circle of medullary rays contains stellate vascular bundles 2–4 mm in diameter that are arranged in a more or less continuous circle in *R. palmatum* or scattered irregularly in *R. officinale* (*9*).

Organoleptic properties

Odour, characteristic aromatic; taste, slightly astringent and bitter; when chewed, gritty between the teeth; colour, yellow-brown to light brown (*1*, *2*).

Microscopic characteristics

The transverse section of the rhizome shows wavy medullary rays, 2–4 cells in width; the xylem consists of a matrix of wood parenchyma and resembles the phloem and cortex regions in that the cells possess either starch, tannin, or large cluster crystals of calcium oxalate. Large, reticulately thickened vessels occur singly or in small groups. Embedded in the parenchyma near the cambium line and mostly in the pith are a number of compound ("stellate") fibrovascular bundles, each of which consists of a small circle of open collateral bundles separated from each other by yellowish brown medullary rays containing anthraquinone derivatives. The bundles differ from the ordinary open collateral bundle in showing phloem inside and xylem outside the cambium. In *R. officinale* the compound bundles ("stellate spots") are scattered through the pith, whereas in *R. palmatum* they are mostly arranged in a ring, the remainder being scattered on either side of the ring (*1*, *2*, *9*, *13*).

Powdered plant material

Powdered Rhizoma Rhei is dusky yellowish orange to moderate yellowish brown, and coloured red in the presence of alkali. Under the microscope, it shows numerous starch grains, spherical, single or 2–4-compound, 2–25 μm in diameter; fragments of non-lignified, reticulate and spiral tracheae, vessels, parenchyma cells containing starch grains or tannin masses; large rosette aggregates of calcium oxalate, 30–60 μm, frequently over 100 μm, and occasionally attaining a diameter of 190 μm; and medullary-ray cells containing an amorphous yellow substance, insoluble in alcohol but soluble in ammonia test solution with a reddish or pink colour; cork, sclerenchymatous cells, and fibres absent (*1*, *2*, *9*, *10*).

Geographical distribution

Rheum officinale and *R. palmatum* are cultivated in China (Gansu, Sichuan, and Qinghai provinces), the Democratic People's Republic of Korea and the Republic of Korea. There are several commercial grades (rhizome with or without rootlets, peeled or unpeeled, in transverse or longitudinal cuts) (*9*, *12*, *14*).

General identity tests

Macroscopic and microscopic examinations; microchemical colour tests and thin-layer chromatographic analysis for the presence of anthraquinones (*1–7*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Rhizoma Rhei products should be negative. The maximum acceptable limits of other microorganisms are as follows (*15–17*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 1.0% (*2–7*).

Total ash

Not more than 12% (*2*, *3*).

Acid-insoluble ash

Not more than 2.0% (*2*, *3*).

Dilute ethanol-soluble extractive

Not less than 30% (*1*).

Moisture

Not more than 12% (*2*, *3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Rhizoma Rhei is not more than 0.05 mg/kg (*17*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residues (*18*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

Chemical and water-soluble extractive tests to be established in accordance with national requirements.

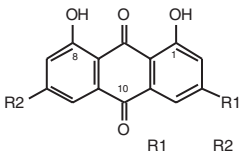
Chemical assays

Contains not less than 2.2% hydroxyanthracene derivatives calculated as rhein (*2*, *3*). Quantitative analysis of total hydroxyanthracene glycosides, calculated as rhein, performed by spectrophotometric analysis (*2*–*7*). High-performance liquid chromatography is also available (*19*) for quantitative analysis.

Thin-layer chromatography is employed for the qualitative analysis for the presence of emodin, physcione (emodin 3-methyl ether), chrysophanol (chrysophanic acid), rhein, and aloe-emodin (*2*, *3*).

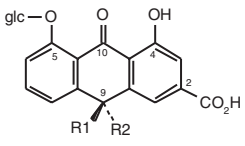
Major chemical constituents

The major constituents are hydroxyanthracene derivatives (2–5%) including emodin, physcione, aloe-emodin, and chrysophanol glycosides, along with di-*O*, *C*-glucosides of the monomeric reduced forms (rheinosides A–D), and dimeric reduced forms (sennosides A–F). The level of the oxidized forms is maximal in the summer and almost nil in the winter (*12*). Until the 1950s, chrysophanol and other anthraquinones were considered to be the constituents producing the purgative action of rhubarb. Current evidence indicates that the major active principles are the dimeric sennosides A–F (*20*).

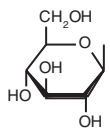


	R1	R2
chrysophanol	CH_3	H
emodin	OH	CH_3
physcione	OCH_3	CH_3
aloe-emodin	CH_2OH	H
rhein *	CO_2H	H

** same numbering as rheinosides*



	R1	R2
rheinoside A	OH	glc **
rheinoside B	glc **	OH
rheinoside C	H	glc **
rheinoside D	glc **	H



** glc = β-D-glucopyranosyl

Dosage forms

Dried plant material and preparations standardized to contain 10–30 mg of hydroxyanthracene derivatives per dose (*21*, *22*). Package in well-closed, light-resistant containers (*9*, *11*).

Medicinal uses

Uses supported by clinical data

Short-term treatment of occasional constipation (*20*, *23*, *24*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

To treat hypotension, increase peripheral vasodilation, and inhibit blood coagulation (*8*, *20*).

Pharmacology

Experimental pharmacology

As shown for senna, the mechanism of action is twofold: (1) stimulation of colonic motility, which augments propulsion and accelerates colonic transit (which in turn reduces fluid absorption from the faecal mass); and (2) an increase in the paracellular permeability across the colonic mucosa probably owing to an inhibition of Na^+/K^+-exchanging ATPase or to an inhibition of chloride channels (*25*, *26*), which results in an increase in the water content in the large intestine (*27*). Purgation is followed by an astringent effect owing to the tannins present (*11*, *12*).

Clinical pharmacology

The active constituents of Rhizoma Rhei are the anthraquinone glycosides, sennosides A–F and rheinosides A–D (*20*). The rheinosides are similar to aloin A and B, the main cathartic principles of *aloe*. The cathartic action of both the sennosides and rheinosides is limited to the large intestine, where they directly increase motor activity in the intestinal tract (*20*, *23*). Consequently, they are seldom effective before 6 hours after oral administration, and they sometimes do not act before 24 hours.

The mechanism of action is similar to that of other anthraquinone stimulant laxatives. Both the sennosides and rheinosides are hydrolysed by intestinal bacteria and then reduced to the active anthrone metabolite, which acts as a stimulant and irritant to the gastrointestinal tract (*28*). Preparations of rhubarb are suitable as an occasional aperient, but should not be used in chronic consti-

pation. A variable amount is absorbed and imparts a yellowish brown colour to the urine, which is changed to a purplish red on the addition of alkali (*11*). Rhizoma Rhei preparations have been employed occasionally for their astringent after effects, to check the diarrhoea produced by irritating substances in the intestines (*11*).

Toxicity

The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes (*29*). Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored, especially in children and the elderly.

Contraindications

As with other stimulant laxatives, products containing Rhizoma Rhei should not be administered to patients with intestinal obstruction and stenosis, atony, severe dehydration states with water and electrolyte depletion, or chronic constipation. Rhizoma Rhei should not be used in patients with inflammatory intestinal diseases, such as appendicitis, Crohn disease, ulcerative colitis, or irritable bowel syndrome, or in children under 10 years of age. Rhizoma Rhei should not be used during pregnancy or lactation except under medical supervision after respective benefits and risks have been considered. As with other stimulant laxatives, Rhizoma Rhei is contraindicated in patients with cramps, colic, haemorrhoids, nephritis, or any undiagnosed abdominal symptoms such as pain, nausea, or vomiting (*23*, *24*).

Warnings

Products containing Rhizoma Rhei should be used only if no effect can be obtained through a change of diet or use of bulk-forming laxatives. Stimulant laxatives should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement after the use of a laxative may indicate a serious condition (*29*). Use of stimulant laxatives for longer than the recommended short-term application may increase intestinal sluggishness (*28*).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.

Chronic use may lead to pseudomelanosis coli (harmless) and to an aggravation of constipation with dependence and possible need for increased dosages.

Chronic abuse with diarrhoea and consequent fluid and electrolyte losses (mainly hypokalaemia) may cause albuminuria and haematuria, and it may result in cardiac and neuromuscular dysfunction, the latter particularly in case of concomitant use of cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root (see below, Precautions).

Precautions

General

Laxatives containing anthraquinone glycosides should not be used for periods longer than 1–2 weeks continually, owing to the danger of electrolyte imbalance (*29*).

Drug interactions

Decreased intestinal transit time may reduce absorption of orally administered drugs (*30*).

Electrolyte imbalances such as increased loss of potassium may potentiate the effects of cardiotonic glycosides (digitalis, strophanthus). Existing hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs, such as quinidine, which affect potassium channels to change sinus rhythm. Simultaneous use with other drugs or herbs which induce hypokalaemia, such as thiazide diuretics, adrenocorticosteroids, or liquorice root, may exacerbate electrolyte imbalance (*22*).

Drug and laboratory test interactions

Anthranoid metabolites may not be detectable with standard methods. Thus results of measuring faecal excretion may not be reliable (*31*). Urinary excretion of certain anthranoid metabolites may discolour the urine, which is not clinically relevant but may cause false positive results for urinary urobilinogen and for estrogens when measured by the Kober procedure (*30*).

Carcinogenesis, mutagenesis, impairment of fertility

Data on the carcinogenicity of Rhizoma Rhei are not available. While chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (*32*, *33*).

Pregnancy: teratogenic effects

The teratogenic effects of Rhizoma Rhei have not been evaluated.

Pregnancy: non-teratogenic effects

Products containing Rhizoma Rhei should not be used by pregnant women because they have a pronounced action on the large intestine and have not undergone sufficient toxicological investigation (*28*).

Nursing mothers

Anthranoid metabolites appear in breast milk. Rhizoma Rhei should not be used during lactation as there are insufficient data available to assess the potential for pharmacological effects in the breast-fed infant (*28*).

Paediatric use

Use of Rhizoma Rhei for children under 10 years of age is contraindicated.

Adverse reactions

Single doses may cause cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage. Overdoses can lead to colicky abdominal spasms and pain and the formation of thin, watery stools (*31*).

Chronic abuse of anthraquinone stimulant laxatives can lead to hepatitis (*34*). Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis, malabsorption, weight loss, albuminuria, and haematuria (*31, 35, 36*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used (*31*). Secondary aldosteronism may occur due to renal tubular damage after aggravated use. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported in laxative abuse (*37*). Melanotic pigmentation of the colonic mucosa (pseudomelanosis coli) has been observed in individuals taking anthraquinone laxatives for extended time periods (*29, 35*). The pigmentation is clinically harmless and usually reversible within 4–12 months after the drug has been discontinued (*30, 35*). Conflicting data exist on other toxic effects such as intestinal-neuronal damage after long-term use (*35*).

Posology

The individually correct dosage is the smallest dosage necessary to maintain a soft stool. The average dose is 0.5–1.5 g of dried plant material or in decoction; preparations standardized to contain 10–30 mg of hydroxyanthracene derivatives, usually taken at bedtime (*21, 22, 28*).

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Folium Sennae

Definition

Folium Sennae consists of the dried leaflets of *Cassia senna* L. (Fabaceae).[1]

Synonyms

Fabaceae are also referred to as Leguminosae.

Although recognized as two distinct species in many pharmacopoeias (*1–8*), *Cassia acutifolia* Delile and *C. angustifolia* Vahl. are considered botanically to be synonyms of the single species *Cassia senna* L. (*9*).

Selected vernacular names

Alexandria senna, Alexandrian senna, cassia, eshrid, falajin, fan xie ye, filaskon maka, hindisana, illesko, Indian senna, ma khaam khaek, makhaam khaek, mecca senna, msahala, nelaponna, nelatangedu, nilavaka, nilavirai, nubia senna, rinji, sanai, sand hijazi, sanjerehi, sen de alejandria, sen de la india, senna makki, senna, senamikki, sennae folium, sona-mukhi, Tinnevelly senna, true senna (*3*, *10–14*).

Description

Low shrubs, up to 1.5 m high, with compound paripinnate leaves, having 3–7 pairs of leaflets, narrow or rounded, pale green to yellowish green. Flowers, tetracyclic, pentamerous, and zygomorphic, have quincuncial calyx, a corolla of yellow petals with brown veins, imbricate ascendent prefloration, and a partially staminodial androeceum. The fruit is a broadly elliptical, somewhat reniform, flattened, parchment-like, dehiscent pod, 4–7 cm long by 2 cm wide, with 6 to 10 seeds (*11*, *14*, *15*).

[1] *C. italica* Mill. is listed in the Malian pharmacopoeia.

Plant material of interest: leaflets

General appearance

Macroscopically, the leaflets are lanceolate or lanceolate-ovate, unequal at the base, with entire margin, acute-mucronate apex and short, stout petioles; sometimes broken; 1.5–5 cm in length and 0.5–1.5 cm in width, bearing a fine pubescence of appressed hairs, more numerous on the lower surface (*1–7*).

Organoleptic properties

The colour is weak yellow to pale olive (*1*, *2*). The odour is characteristic, and the taste is mucilage-like and then slightly bitter (*1*, *3*).

Microscopic characteristics

Epidermis with polygonal cells containing mucilage; unicellular thick-walled trichomes, length, up to 260 µm, slightly curved at the base, warty; paracytic stomata on both surfaces; under the epidermal cells a single row of palisade layer; cluster crystals of calcium oxalate distributed throughout the lacunose tissue; on the adaxial surface, sclerenchymatous fibres and a gutter-shaped group of similar fibres on the abaxial side containing prismatic crystals of calcium oxalate (*1*).

Powdered plant material

Light green to greenish yellow. Polygonal epidermal cells showing paracytic stomata. Unicellular trichomes, conical in shape, with warty walls, isolated or attached to fragments of epidermis. Fragments of fibrovascular bundles with a crystal sheath containing calcium oxalate prisms. Cluster crystals isolated or in fragments of parenchyma (*2*, *3*).

Geographical distribution

The plant is indigenous to tropical Africa. It grows wild near the Nile river from Aswan to Kordofan, and in the Arabian peninsula, India and Somalia (*15*). It is cultivated in India, Pakistan, and the Sudan (*11*, *12*, *14*, *15*).

General identity tests

Macroscopic, microscopic examinations, and microchemical analysis (*1–6*), and thin-layer chromatographic analysis for the presence of characteristic sennosides (sennosides A–D) (*3–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Folium Sennae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*16–18*). For

preparation of decoction: aerobic bacteria—10^7/g; moulds and yeast—10^5/g; *Escherichia coli*—10^2/g; other enterobacteria—10^4/g. Preparations for internal use: aerobic bacteria—10^5/g; moulds and yeast—10^4/g; *Escherichia coli*—0/g; other enterobacteria—10^3/g.

Foreign organic matter

Not more than 2.0% of stems (*1*) and not more than 1.0% of other foreign organic matter (*1*, *4*, *8*).

Total ash

Not more than 12% (*5*).

Acid-insoluble ash

Not more than 2.0% (*1*, *8*).

Water-soluble extractive

Not less than 3% (*1*).

Moisture

Not more than 10% (*6*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Folium Sennae is not more than 0.05 mg/kg (*18*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*16*) and guidelines for predicting dietary intake of pesticide residues (*19*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*16*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*16*).

Other purity tests

Chemical tests and tests of alcohol-soluble extractive are to be established in accordance with national requirements.

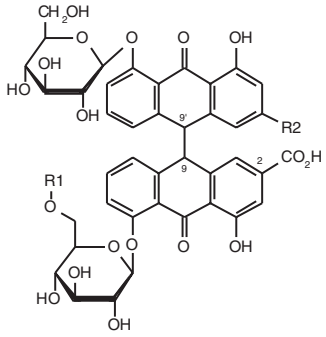
Chemical assays

Contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B (*1, 4, 5*). Quantitative analysis is performed by spectrophotometry (*1, 4–8*) and by high-performance liquid chromatography (*20*).

Thin-layer chromatography is employed for qualitative analysis for the presence of sennosides A and B (*3–5*).

Major chemical constituents

Folium Sennae contains a family of hydroxyanthracene glycosides, the most plentiful of which are sennosides A and B. There are also small amounts of aloe-emodin and rhein 8-glucosides, mucilage, flavonoids, and naphthalene precursors (*15*).



	R1	R2	9-9'
sennoside A	H	CO_2H	*R*,R* (threo)*
sennoside B	H	CO_2H	*R*,S* (erythro)*
sennoside C	H	CH_2OH	*R*,R* (threo)*
sennoside D	H	CH_2OH	*R*,S* (erythro)*
sennoside E	CO-CO_2H	CO_2H	*R*,R* (threo)*
sennoside F	CO-CO_2H	CO_2H	*R*,S* (erythro)*

Dosage forms

Crude plant material, powder, oral infusion, and extracts (liquid or solid) standardized for content of sennosides A and B (*15, 21, 22*). Package in well-closed containers protected from light and moisture (*1–8*).

Medicinal uses

Uses supported by clinical data

Short-term use in occasional constipation (*21–25*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

As an expectorant, a wound dressing, an antidysenteric, and a carminative agent; and for the treatment of gonorrhoea, skin diseases, dyspepsia, fever, and haemorrhoids (*11*, *23*, *25*).

Pharmacology

Experimental pharmacology

The effects of Folium Sennae are due primarily to the hydroxyanthracene glucosides, especially sennosides A and B. These β-linked glucosides are secretagogues that increase net secretion of fluids and specifically influence colonic motility and enhance colonic transit. They are not absorbed in the upper intestinal tract; they are converted by the bacteria of the large intestine into the active derivatives (rhein-anthrone). The mechanism of action is twofold: (1) effect on the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions), resulting in an accelerated colonic transit, thereby reducing fluid absorption, and (2) an influence on fluid and electrolyte absorption and secretion by the colon (stimulation of mucus and active chloride secretion), increasing fluid secretion (*24*, *25*).

Clinical pharmacology

The time of action of senna is usually 8–10 hours, and thus the dose should be taken at night (*24*). The action of the sennosides augments, without disrupting, the response to the physiological stimuli of food and physical activity (*24*). The sennosides abolish the severe constipation of patients suffering from severe irritable bowel syndrome (*26*). In therapeutic doses, the sennosides do not disrupt the usual pattern of defecation times and markedly soften the stool (*24*). Sennosides significantly increase the rate of colonic transit (*27*) and increase colonic peristalsis, which in turn increase both faecal weight and dry bacterial mass (*24*, *28*). Due to their colonic specificity, the sennosides are poorly absorbed in the upper gastrointestinal tract (*29*).

Toxicity

The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored, especially in children and the elderly.

Contraindications

As with other stimulant laxatives, the drug is contraindicated in persons with ileus, intestinal obstruction, and stenosis, atony, undiagnosed abdominal symptoms, inflammatory colonopathies, appendicitis, abdominal pains of unknown

cause, severe dehydration states with water and electrolyte depletion, or chronic constipation (*21*, *30*). Folium Sennae should not be used in children under the age of 10 years.

Warnings

Stimulant laxative products should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition (*31*). Chronic abuse, with diarrhoea and consequent fluid electrolyte losses, may cause dependence and need for increased dosages, disturbance of the water and electrolyte balance (e.g. hypokalaemia), atonic colon with impaired function, albuminuria and haematuria (*29*, *32*).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.

Chronic use may lead to pseudomelanosis coli (harmless).

Hypokalaemia may result in cardiac and neuromuscular dysfunction, especially if cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root are taken (*29*).

Precautions

General

Use for more than 2 weeks requires medical attention (*21*, *31*).

Drug interactions

Decreased intestinal transit time may reduce absorption of orally administered drugs (*32*, *33*).

The increased loss of potassium may potentiate the effects of cardiotonic glycosides (digitalis, strophanthus). Existing hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs, such as quinidine, which affect potassium channels to change sinus rhythm. Simultaneous use with other drugs or herbs which induce hypokalaemia, such as thiazide diuretics, adrenocorticosteroids, or liquorice root, may exacerbate electrolyte imbalance (*21*, *22*).

Drug and laboratory test interactions

Urine discoloration by anthranoid metabolites may lead to false positive test results for urinary urobilinogen, and for estrogens measured by the Kober procedure (*32*).

Carcinogenesis, mutagenesis, impairment of fertility

No *in vivo* genotoxic effects have been reported to date (*34*–*37*). Although chronic abuse of anthranoid-containing laxatives was hypothesized to play a

role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (*38–40*).

Pregnancy: non-teratogenic effects

Use during pregnancy should be limited to conditions in which changes in diet or fibre laxatives are not effective (*41*).

Nursing mothers

Use during breast-feeding is not recommended owing to insufficient data on the excretion of metabolites in breast milk (*21*). Small amounts of active metabolites (rhein) are excreted into breast milk, but a laxative effect in breast-fed babies has not been reported (*21*).

Paediatric use

Contraindicated for children under 10 years of age (*21*).

Other precautions

No information available on teratogenic effects in pregnancy.

Adverse reactions

Senna may cause mild abdominal discomfort such as colic or cramps (*21*, *22*, *33*). A single case of hepatitis has been described after chronic abuse (*42*). Melanosis coli, a condition which is characterized by pigment-loaded macrophages within the submucosa, may occur after long-term use. This condition is clinically harmless and disappears with cessation of treatment (*33*, *43*, *44*).

Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis or alkalosis, malabsorption, weight loss, albuminuria, and haematuria (*21*, *22*, *33*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used (*21*, *33*). Conflicting data exist on other toxic effects such as intestinal-neuronal damage due to long-term misuse (*45–54*).

Posology

The correct individual dose is the smallest required to produce a comfortable, soft-formed motion (*21*). Powder: 1–2 g of leaf daily at bedtime (*11*). Adults and children over 10 years: standardized daily dose equivalent to 10–30 mg sennosides (calculated as sennoside B) taken at night.

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Fructus Sennae

Definition

Fructus Sennae consists of the dried ripe fruit of *Cassia senna* L. (Fabaceae).[1]

Synonyms

Fabaceae are also referred to as Leguminosae.

Cassia acutifolia Delile and *Cassia angustifolia* Vahl. (*1*) are recognized as two distinct species in a number of pharmacopoeias as Alexandrian senna fruit and Tinnevelly senna fruit (*2–7*). Botanically, however, they are considered to be synonyms of the single species *Cassia senna* L. (*1*).

Selected vernacular names

Alexandria senna, Alexandrian senna, cassia, eshrid, falajin, fan xie ye, filaskon maka, hindisana, illesko, Indian senna, ma khaam khaek, makhaam khaek, Mecca senna, msahala, nelaponna, nelatangedu, nilavaka, nilavirai, nubia senna, rinji, sanai, sand hijazi, sanjerehi, sen de Alejandria, sen de la India, senna makki, senna, senna pod, senamikki, sona-mukhi, Tinnevelly senna, true senna (*8–11*).

Description

Low shrubs, up to 1.5 m high, with compound paripinnate leaves, having 3–7 pairs of leaflets, narrow or rounded, pale green to yellowish green. Flowers, tetracyclic, pentamerous and zygomorphic, have quincuncial calyx, a corolla of yellow petals with brown veins, imbricate ascendent prefloration, and a partially staminodial androeceum. The fresh fruit is a broadly elliptical, somewhat reniform, flattened, parchment-like, dehiscent pod, 4–7 cm long by 2 cm wide, with 6–10 seeds (*9*, *12*, *13*).

Plant material of interest: dried ripe fruit

General appearance

Fructus Sennae is leaf-like, has flat and thin pods, yellowish green to yellowish brown with a dark brown central area, oblong or reniform. Fruit is pale to greyish green, 3.5–6.0 cm in length, 1.4–1.8 cm in width; stylar point at one end,

[1] *Cassia italica* Mill. is listed in the Malian pharmacopoeia.

containing 6–10 obovate green to pale brown seeds with longitudinal prominent ridges on the testa (*2*).

Organoleptic properties

Colour is pale green to brown to greyish black (*2, 3*); odour, characteristic; taste, mucilaginous and then slightly bitter (*2*).

Microscopic characteristics

Epicarp with very thick cuticularized isodiametrical cells, occasional anomocytic or paracytic stomata, and very few unicellular and warty trichomes; hypodermis with collenchymatous cells; mesocarp with parenchymatous tissue containing a layer of calcium oxalate prisms; endocarp consisting of thick-walled fibre, mostly perpendicular to the longitudinal axis of the fruit, but the inner fibres running at an oblique angle or parallel to the longitudinal axis. Seeds, subepidermal layer of palisade cells with thick outer walls; the endosperm has polyhedral cells with mucilaginous walls (*2*).

Powdered plant material

Brown; epicarp with polygonal cells and a small number of conical warty trichomes and occasional anomocytic or paracytic stomata; fibres in two crossed layers accompanied by a crystal sheath of calcium oxalate prisms; characteristic palisade cells in the seeds and stratified cells in the endosperm; clusters and prisms of calcium oxalate (*4*).

Geographical distribution

The plant is indigenous to tropical Africa. It grows wild near the Nile river from Aswan to Kordofan, and in the Arabian peninsula, India, and Somalia (*12, 13*). It is cultivated in India, Pakistan, and the Sudan (*8, 9, 11–14*).

General identity tests

Macroscopic, microscopic, and microchemical examinations (*2–7*), and thin-layer chromatographic analysis for the presence of characteristic sennosides (sennosides A–D).

Purity tests

Microbiology

The test for *Salmonella* spp. in Fructus Sennae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*15–17*). For preparation of decoction: aerobic bacteria—10^7/g; moulds and yeast—10^5/g; *Escherichia coli*—10^2/g; other enterobacteria—10^4/g. Preparations for internal use: aerobic bacteria—10^5/g or ml; moulds and yeast—10^4/g or ml; *Escherichia coli*—0/g or ml; other enterobacteria—10^3/g or ml.

Foreign organic matter

Not more than 1.0% (*2*).

Total ash

Not more than 6% (*3*).

Acid-insoluble ash

Not more than 2.0% (*2*, *4*, *5*).

Water-soluble extractive

Not less than 25% (*2*).

Moisture

Not more than 12% (*5*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Fructus Sennae is not more than 0.05 mg/kg (*17*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residues (*18*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

Chemical tests and tests of alcohol-soluble extractive to be established in accordance with national requirements.

Chemical assays

Contains not less than 2.2% of hydroxyanthracene glycosides, calculated as sennoside B (*2–7*). Quantitative analysis is performed by spectrophotometry (*2*, *5–7*) or by high-performance liquid chromatography (*19*).

The presence of sennosides A and B (*3–5*) can be determined by thin-layer chromatography.

Major chemical constituents

Fructus Sennae contains a family of hydroxyanthracene glycosides, the most plentiful of which are sennosides A and B (for structures, see page 244). There are also small amounts of aloe-emodin and rhein 8-glucosides, mucilage, flavonoids, and naphthalene precursors (*12*, *13*, *20*).

Dosage forms

Crude plant material, powder, oral infusion, and extracts (liquid or solid, standardized for content of sennosides A and B) (*12*, *20*, *21*). Package in well-closed containers protected from light and moisture (*2–7*).

Medicinal uses

Uses supported by clinical data

Short-term use in occasional constipation (*21–25*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

As an expectorant, a wound dressing, an antidysenteric, and a carminative agent; and for the treatment of gonorrhoea, skin diseases, dyspepsia, fever, and haemorrhoids (*11*, *23*, *25*).

Pharmacology

Experimental pharmacology

The effects of Fructus Sennae are due primarily to the hydroxyanthracene glucosides, especially sennosides A and B. These β-linked glucosides are secretagogues that induce net secretion of fluids, and specifically influence colonic motility and enhance colonic transit. They are not absorbed in the upper intestinal tract; they are converted by the bacteria of the large intestine into the active derivatives (rhein-anthrone). The mechanism of action is twofold: an effect on the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions), which accelerates colonic transit, thereby reducing fluid absorption; and an influence on fluid and electrolyte absorption and secretion by the colon (stimulation of mucus and active chloride secretion), which increases fluid secretion (*24*, *25*).

Clinical pharmacology

The time of action of Senna is usually 8–10 hours, and thus the dose should be taken at night (*24*). The action of the sennosides augments, without disrupting, the response to the physiological stimuli of food and physical activity (*24*). The

sennosides abolish the severe constipation of patients suffering from severe irritable bowel syndrome (*26*). In therapeutic doses, the sennosides do not disrupt the usual pattern of defecation times and markedly soften stools (*24*). Sennosides significantly increase the rate of colonic transit (*27*) and increase colonic peristalsis, which in turn increases both faecal weight and dry bacterial mass (*24, 28*). Due to their colonic specificity, the sennosides are poorly absorbed in the upper gastrointestinal tract (*29*).

Toxicity

The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored, especially in children and the elderly.

Contraindications

As with other stimulant laxatives, the drug is contraindicated in cases of ileus, intestinal obstruction, stenosis, atony, undiagnosed abdominal symptoms, inflammatory colonopathies, appendicitis, abdominal pains of unknown cause, severe dehydration states with water and electrolyte depletion, or chronic constipation (*20, 21, 30*). Fructus Sennae should not be used in children under the age of 10 years.

Warnings

Stimulant laxative products should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition (*31*). Chronic abuse with diarrhoea and consequent fluid and electrolyte losses may cause dependence and need for increased dosages, disturbance of the water and electrolyte balance (e.g. hypokalaemia), atonic colon with impaired function and albuminuria and haematuria (*21, 32*).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.

Chronic use may lead to pseudomelanosis coli (harmless).

Hypokalaemia may result in cardiac and neuromuscular dysfunction, especially if cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root are taken (*29*).

Precautions

General

Use for more than 2 weeks requires medical attention (*21, 31*).

Drug interactions

Decreased intestinal transit time may reduce absorption of orally administered drugs (*32, 33*).

The increased loss of potassium may potentiate the effects of cardiotonic glycosides (digitalis, strophanthus). Existing hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs, such as quinidine, which affect potassium channels to change sinus rhythm. Simultaneous use with other drugs or herbs which induce hypokalaemia, such as thiazide diuretics, adrenocorticosteroids, or liquorice root, may exacerbate electrolyte imbalance (*20*, *21*).

Drug and laboratory test interactions

Urine discoloration by anthranoid metabolites may lead to false positive test results for urinary urobilinogen and for estrogens measured by the Kober procedure (*32*).

Carcinogenesis, mutagenesis, impairment of fertility

No *in vivo* genotoxic effects have been reported to date (*34–37*). Although chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (*38–40*).

Pregnancy: non-teratogenic effects

Use during pregnancy should be limited to conditions in which changes in diet or fibre laxatives are not effective (*41*).

Nursing mothers

Use during breast-feeding is not recommended owing to insufficient available data on the excretion of metabolites in breast milk (*21*). Small amounts of active metabolites (rhein) are excreted into breast milk, but a laxative effect in breast-fed babies has not been reported (*21*).

Paediatric use

Contraindicated for children under 10 years of age (*21*).

Other precautions

No information available concerning teratogenic effects on pregnancy.

Adverse reactions

Senna may cause mild abdominal discomfort such as colic or griping (*21*, *22*, *33*). A single case of hepatitis has been described after chronic abuse (*42*). Melanosis coli, a condition which is characterized by pigment-loaded macrophages within the submucosa, may occur after long-term use. This condition is clinically harmless and disappears with cessation of treatment (*33*, *43*, *44*).

Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis or alkalosis, malabsorption,

weight loss, albuminuria, and haematuria (*21*, *22*, *33*). Weakness and orthostatic hypotension may be exacerbated in elderly patients who repeatedly use stimulant laxatives (*21*, *33*). Conflicting data exist on other toxic effects such as intestinal-neuronal damage after long-term misuse (*45–54*).

Posology

The correct individual dose is the smallest required to produce a comfortable, soft-formed motion (*21*). Powder, 1–2 g of fruit daily at bedtime (*8*, *19*, *20*). Adults and children over 10 years: standardized daily dose equivalent to 10–30 mg sennosides (calculated as sennoside B) taken at night.

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Herba Thymi

Definition

Herba Thymi is the dried leaves and flowering tops of *Thymus vulgaris* L. or of *Thymus zygis* L. (Lamiaceae) (*1*, *2*).

Synonyms

Lamiaceae are also known as Labiatae.

Selected vernacular names

Common thyme, farigola, garden thyme, herba timi, herba thymi, mother of thyme, red thyme, rubbed thyme, ten, thick leaf thyme, thym, Thymian, thyme, time, timi, tomillo, za'ater (*1*, *3–7*).

Description

An aromatic perennial sub-shrub, 20–30 cm in height, with ascending, quadrangular, greyish brown to purplish brown lignified and twisted stems bearing oblong-lanceolate to ovate-lanceolate greyish green leaves that are pubescent on the lower surface. The flowers have a pubescent calyx and a bilobate, pinkish or whitish, corolla and are borne in verticillasters. The fruit consists of 4 brown ovoid nutlets (*5*, *8*, *9*).

Plant material of interest: dried leaves and flowering tops

General appearance

Thymus vulgaris

Leaf 4–12 mm long and up to 3 mm wide; it is sessile or has a very short petiole. The lamina is tough, entire, lanceolate to ovate, covered on both surfaces by a grey to greenish grey indumentum; the edges are markedly rolled up towards the abaxial surface. The midrib is depressed on the adaxial surface and is very prominent on the abaxial surface. The calyx is green, often with violet spots, and is tubular; at the end are 2 lips of which the upper is bent back and has 3 lobes on its end; the lower is longer and has 2 hairy teeth. After flowering, the calyx tube is closed by a crown of long, stiff hairs. The corolla, about twice as long as the calyx, is usually brownish in the dry state and is slightly bilabiate (*1*).

Thymus zygis

Leaf 1.7–6.5 mm long and 0.4–1.2 mm wide; it is acicular to linear-lanceolate and the edges are markedly rolled toward the abaxial surface. Both surfaces of the lamina are green to greenish grey and the midrib is sometimes violet; the edges, in particular at the base, have long, white hairs. The dried flowers are very similar to those of *Thymus vulgaris* (*1*).

Organoleptic properties

Odour and taste aromatic (*1–3*, *5*).

Microscopic characteristics

In leaf upper epidermis, cells tangentially elongated in transverse section with a thick cuticle and few stomata, somewhat polygonal in surface section with beaded vertical walls and striated cuticle, the stoma being at a right angle to the 2 parallel neighbouring cells. Numerous unicellular, non-glandular hairs up to 30 μm in length with papillose wall and apical cell, straight, or pointed, curved, or hooked. Numerous glandular hairs of two kinds, one with a short stalk embedded in the epidermal layer and a unicellular head, the other with an 8- to 12-celled head and no stalk. Palisade parenchyma of 2 layers of columnar cells containing many chloroplastids; occasionally an interrupted third layer is present. Spongy parenchyma of about 6 layers of irregular-shaped chlorenchyma cells and intercellular air-spaces (*5*).

Powdered plant material

Grey-green to greenish brown powder; leaf fragments, epidermal cells prolonged into unicellular pointed, papillose trichomes, 60 μm long; trichomes of the lower surface uniseriate, 2–3 celled, sharp pointed, up to 300 μm in diameter, numerous labiate trichomes with 8–12 secretory cells up to 80 μm in diameter; broadly elliptical caryophyllaceous stomata. Six- to 8-celled uniseriate trichomes from the calyx up to 400 μm long; pollen grains spherical; pericyclic fibres of the stem (*1–3*).

Geographical distribution

Indigenous to southern Europe. It is a pan-European species that is cultivated in Europe, the United States of America and other parts of the world (*2*, *3*, *5*, *10*).

General identity tests

Macroscopic and microscopic examinations (*1*, *5*), and chemical and thin-layer chromatography tests for the characteristic volatile oil constituent, thymol [**1**].

Purity tests

Microbiology

The test for *Salmonella* spp. in Herba Thymi products should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). For preparation of infusion: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for oral use: aerobic bacteria—not more than 10^5/ml; fungi—not more than 10^4/ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/ml; *Escherichia coli*—0/ml.

Foreign organic matter

Not more than 10% of stem having a diameter up to 1 mm. Leaves with long trichomes at their base and with weakly pubescent other parts not allowed (*1*). The leaves and flowering tops of *Origanum creticum* or *O. dictamnus* are considered adulterants (*3*, *5*). Other foreign organic matter, not more than 2% (*2*).

Total ash

Not more than 15% (*1*).

Acid-insoluble ash

Not more than 2.0% (*1*).

Moisture

Not more than 10% (*1*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Thymi is not more than 0.05 mg/kg (*13*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*14*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

Chemical, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

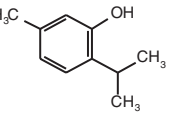
Chemical assays

Herba Thymi contains not less than 1.0% volatile oil (*2*, *3*), and not less than 0.5% phenols. Volatile oil is quantitatively determined by water/steam distillation (*1*), and the percentage content of phenols expressed as thymol is determined by spectrophotometric analysis (*1*). Thin-layer chromatographic analysis is used for thymol, carvacrol, and linalool (*1*, *15*).

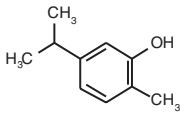
Major chemical constituents

Herba Thymi contains about 2.5% but not less than 1.0% of volatile oil. The composition of the volatile oil fluctuates depending on the chemotype under consideration. The principal components of Herba Thymi are thymol [**1**] and carvacrol [**2**] (up to 64% of oil), along with linalool, *p*-cymol, cymene, thymene, α-pinene, apigenin, luteolin, and 6-hydroxyluteolin glycosides, as well as di-, tri- and tetramethoxylated flavones, all substituted in the 6-position (for example 5,4′-dihydroxy-6,7-dimethoxyflavone, 5,4′-dihydroxy-6,7,3′-trimethoxyflavone and its 8-methoxylated derivative 5,6,4′-trihydroxy-7,8,3′-trimethoxyflavone) (*1*, *3*–*6*, *9*).

thymol **[1]**



carvacrol **[2]**



Dosage forms

Dried herb for infusion, extract, and tincture (*1*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Thyme extract has been used orally to treat dyspepsia and other gastrointestinal disturbances; coughs due to colds, bronchitis and pertussis; and laryngitis and tonsillitis (as a gargle). Topical applications of thyme extract have been used in the treatment of minor wounds, the common cold, disorders of the oral cavity, and as an antibacterial agent in oral hygiene (*3*, *5*, *8*, *15*, *16*). Both the essential oil and thymol are ingredients of a number of proprietary drugs including antiseptic and healing ointments, syrups for the treatment of respiratory disorders, and preparations for inhalation. Another species in the genus, *T. serpyllum* L., is used for the same indications (*8*).

Uses described in folk medicine, not supported by experimental or clinical data

As an emmenagogue, sedative, antiseptic, antipyretic, to control menstruation and cramps, and in the treatment of dermatitis (*7*).

Pharmacology

Experimental pharmacology

Spasmolytic and antitussive activities

The spasmolytic and antitussive activity of thyme has been most often attributed to the phenolic constituents thymol and carvacrol, which make up a large percentage of the volatile oil (*17*). Although these compounds have been shown to prevent contractions induced in the ileum and the trachea of the guinea-pig, by histamine, acetylcholine and other reagents, the concentration of phenolics in aqueous preparations of the drug is insufficient to account for this activity (*18*, *19*). Experimental evidence suggests that the *in vitro* spasmolytic activity of thyme preparations is due to the presence of polymethoxyflavones (*10*). *In vitro* studies have shown that flavones and thyme extracts inhibit responses to agonists of specific receptors such as acetylcholine, histamine and L-norepinephrine, as well as agents whose actions do not require specific receptors, such as barium chloride (*10*). The flavones of thyme were found to act as non-competitive and non-specific antagonists (*10*); they were also shown to be Ca^{2+} antagonists and musculotropic agents that act directly on smooth muscle (*10*).

Expectorant and secretomotor activities

Experimental evidence suggests that thyme oil has secretomotoric activity (*20*). This activity has been associated with a saponin extract from *T. vulgaris* (*21*). Stimulation of ciliary movements in the pharynx mucosa of frogs treated with diluted solutions of thyme oil, thymol or carvacrol has also been reported (*22*). Furthermore, an increase in mucus secretion of the bronchi after treatment with thyme extracts has been observed (*23*).

Antifungal and antibacterial activities

In vitro studies have shown that both thyme essential oil and thymol have antifungal activity against a number of fungi, including *Cryptococcus neoformans*, *Aspergillus*, *Saprolegnia*, and *Zygorhynchus* species (*24–27*). Both the essential oil and thymol had antibacterial activity against *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, and a number of other bacterial species (*28*, *29*). As an antibiotic, thymol is 25 times as effective as phenol, but less toxic (*30*).

Contraindications

Pregnancy and lactation (See Precautions, below).

Warnings

No information available.

Precautions

General

Patients with a known sensitivity to plants in the Lamiaceae (Labiatae) should contact their physician before using thyme preparations. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Thyme essential oil did not have any mutagenic activity in the *Bacillus subtilis rec*-assay or the *Salmonella*/microsome reversion assay (*32*, *33*). Recent investigations suggest that thyme extracts are antimutagenic (*34*) and that luteolin, a constituent of thyme, is a strong antimutagen against the dietary carcinogen Trp-P-2 (*35*).

Pregnancy: non-teratogenic effects

The safety of Herba Thymi preparations during pregnancy or lactation has not been established. As a precautionary measure, the drug should not be used during pregnancy or lactation except on medical advice. However, widespread use of Herba Thymi has not resulted in any safety concerns.

Nursing mothers

See Pregnancy: non-teratogenic effects, above.

Other precautions

No information available concerning drug interactions, drug and laboratory test interactions, paediatric use, or teratogenic effects on pregnancy.

Adverse reactions

Contact dermatitis has been reported. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (*31*).

Posology

Adults and children from 1 year: 1–2 g of the dried herb or the equivalent amount of fresh herb as an oral infusion several times a day (*30*, *36*); children up to 1 year: 0.5–1 g (*36*). Fluid extract: dosage calculated according to the dosage of the herb (*37*). Tincture (1 : 10, 70% ethanol): 40 drops up to 3 times daily (*38*). Topical use: a 5% infusion as a gargle or mouth-wash (*30*, *38*).

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Radix Valerianae

Definition

Radix Valerianae consists of the subterranean parts of *Valeriana officinalis* L. *(sensu lato)* (Valerianaceae)[1] including the rhizomes, roots, and stolons, carefully dried at a temperature below 40 °C (*1–6*).

Synonyms

Valeriana alternifolia Ledeb., *Valeriana excelsa* Poir., *Valeriana sylvestris* Grosch. (*1*).

Selected vernacular names

All heal, akar pulepandak, amantilla, balderbrackenwurzel, baldrian, Baldrianwurzel, cat's love, cat's valerian, fragrant valerian, garden heliotrope, great wild valerian, ka-no-ko-so, Katzenwurzel, kesso root, kissokon, kuanyexiccao, luj, nard, ntiv, racine de valeriane, St. George's herb, setwall, txham laaj, valerian fragrant, valerian, valeriana, valeriana extranjera, valeriana rhizome, valeriane, vandal root, waliryana, wild valerian (*8–11*).

Descriptions

A tall perennial herb whose underground portion consists of a vertical rhizome bearing numerous rootlets and one or more stolons. The aerial portion consists of a cylindrical hollow, channelled stem attaining 2 m in height, branched in the terminal region, bearing opposite exstipulate, pinnatisect, cauline leaves with clasping petioles. The inflorescence consists of racemes of cymes whose flowers are small, white, or pink. The fruits are oblong-ovate, 4-ridged, single-seeded achenes (*1*, *9*).

Valeriana officinalis (*sensu lato*) is an extremely polymorphous complex of subspecies. The basic type is diploid, $2n = 14$, (*V. officinalis*) and other subspecies have very similar characteristics: *V. officinalis* ssp. *collina* (Wallr.) Nyman

[1] Approximately 200 *Valeriana* species are available, but only a few are or were used medicinally, such as *V. fauriei* Briquet (Japanese Valerian) (*7*), *V. wallichii* DC (Indian Valerian) and *V. edulis* Nutt ex. Torr. & Gray (*8*). In commerce, *V. edulis* Nutt. ex Torr. & Gray is known as "Valeriana mexicana". Plants bearing this common name should not be confused with *V. mexicana* DC., which is in fact *V. sorbifolia* H.B.K. var. *mexicana* (DC) F.G. Mey.

($2n = 28$) has leaves with 15–27 folioles, all of the same width, and *V. officinalis* ssp. *sambucifolia* (Mikan f.) Celak, *V. excelsa* Poiret ($2n = 56$) has leaves with 5–9 folioles, with the apical one clearly larger than the others. In contrast to the other subspecies, the rhizome of the latter is clearly stoloniferous (epigenous and hypnogenous stolons). *V. repens* Host. (equivalent to *V. procurrens* Wallr.) could be considered a fourth species, according to the Flora Europaea. Often appended to this species are taxonomic groups of uncertain status and limited distribution (e.g. *V. salina* Pleigel or *V. versifolia* Brügger) (*12*).

Plant material of interest: dried roots, rhizomes and stolons

General appearance

Rhizome, erect, entire or usually cut into 2–4 longitudinal pieces, 2–5 cm long, 1–3 cm thick; externally, dull yellowish brown or dark brown, sometimes crowned by the remains of stem bases and scale leaves, and bears occasional, short, horizontal branches (stolons), and numerous rootlets or their circular scars; fracture, short and horny. Internally, whitish, with an irregular outline, occasionally hollow and exhibiting a comparatively narrow ark traversed, here and there, by root-traces, and separated by a dark line, the cambium, from a ring, small xylem bundles surrounding a central pith. Roots, numerous, slender, cylindrical, usually plump; 2–12 cm but mostly 8–10 cm long, 0.5–2 mm in diameter; externally, greyish brown to brownish yellow, longitudinally striated, with fibrous lateral rootlets; brittle; internally, showing a wide bark and a narrow central stele (*1*, *9*).

Organoleptic properties

Odour, characteristic, penetrating valeric acid-like, becoming stronger on aging; taste, sweetish initially, becoming camphoraceous and somewhat bitter (*1–5*, *9*).

Microscopic characteristics

Rhizome, with epidermis of polygonal cells, having the outer walls slightly thickened; cork, immediately below the epidermis, of up to 7 layers of slightly suberized, brownish, large polygonal cells; cortex, parenchymatous with rather thick-walled parenchyma, containing numerous starch granules and traversed by numerous root-traces; endodermis of a single layer of tangentially elongated cells containing globules of volatile oil; pericycle, parenchymatous; vascular bundles, collateral, in a ring and surrounding a very large parenchymatous pith, containing starch granules and occasional scattered groups of sclereids with thick pitted walls and narrow lumen; xylem, with slender, annular, spiral, and pitted vessels, in small numbers. Branches similar to rhizome but with a prominent endodermis and a well-defined ring of vascular bundles, showing secondary thickening.

Root, with piliferous layer, of papillosed cells, some developed into root hairs; exodermis, or a single layer of quadrangular to polygonal cells, with suberized walls, and containing globules of volatile oil; cortex, parenchymatous, with numerous starch granules, the outermost cells containing globules of volatile oil; endodermis, of 1 layer of cells with thickened radial walls; primary xylem, of 3–11 arches surrounding a small central parenchymatous pith containing starch granules, 5–15 μm in diameter, sometimes showing a cleft or stellate hilum; the compound granules, with 2–6 components, up to 20 μm in diameter. Older roots show a pith of starch-bearing parenchyma, vascular bundles with secondary thickening and a periderm originating in the piliferous layer (*1*, *4*, *9*, *13*).

Powdered plant material

Light brown and characterized by numerous fragments of parenchyma with round or elongated cells and containing starch granules, 5–15 μm in diameter, sometimes showing a cleft or stellate hilum, the compound granules, with 2–6 components, up to 20 μm in diameter; cells containing light brown resin; rectangular sclereids with pitted walls, 5–15 μm thick; xylem, isolated or in noncompact bundles, 10–50 μm in diameter; some absorbing root hairs and cork fragments are also present (*4*).

Geographical distribution

Valeriana officinalis (*sensu lato*) is an extremely polymorphous complex of subspecies with natural populations dispersed throughout temperate and sub-polar Eurasian zones. The species is common in damp woods, ditches, and along streams in Europe, and is cultivated as a medicinal plant, especially in Belgium, England, eastern Europe, France, Germany, the Netherlands, the Russian Federation, and the United States of America (*1*, *9*, *10*, *12*).

General identity tests

Macroscopic, microscopic, organoleptic, and microchemical examination (*1–6*, *9*, *13*); and by thin-layer chromatography for the presence of valerenic acid, acetoxyvalerenic acid, valtrate, and isovaltrate (*1–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Valerianae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*14–16*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more

than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 5% (*1*).

Acid-insoluble ash

Not more than 7% (*1–5*).

Dilute ethanol-soluble extractive

Not less than 15% (*2–5*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Valerianae is not more than 0.05 mg/kg (*16*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*14*) and guidelines for predicting dietary intake of pesticide residues (*17*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*14*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*14*).

Other purity tests

Chemical, moisture, total ash and water-soluble extractive tests are to be established in accordance with national standards.

Chemical assays

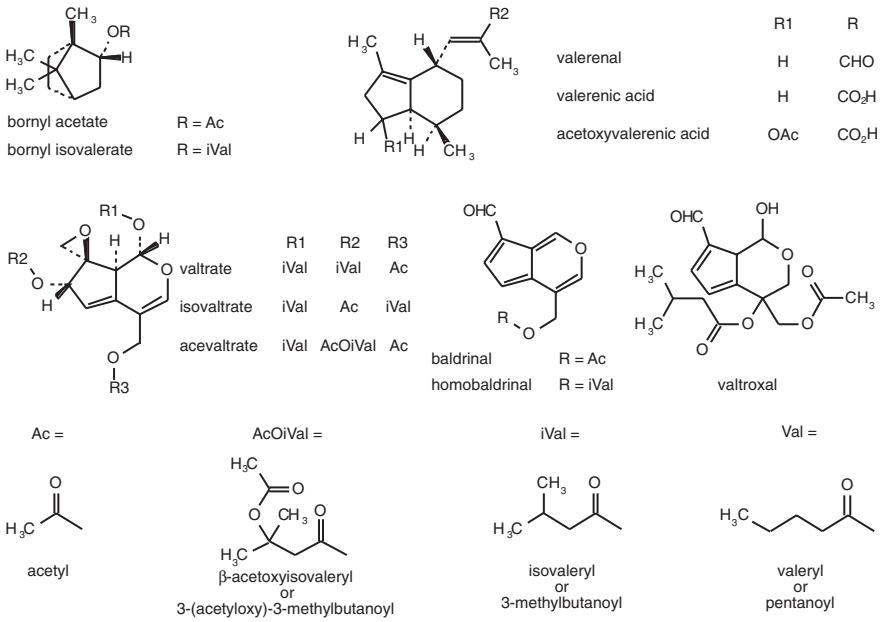
Contains not less than 0.5% v/w of essential oil (*3–5*), quantitatively determined by distillation (*2–5*). Content of individual constituents including valepotriates, valerenic acids and valerenal, determined by high-performance liquid (*18, 19*) or gas–liquid (*20*) chromatographic methods.

Major chemical constituents

The chemical composition of Radix Valerianae varies greatly depending on the subspecies, variety, age of the plant, growing conditions, and type and age of the extract. The volatile oil (ranges 0.2–2.8%) contains bornyl acetate and

bornyl isovalerate as the principal components. Other significant constituents include β-caryophyllene, valeranone, valerenal, valerenic acid, and other sesquiterpenoids and monoterpenes (*12*, *21*). The co-occurrence of three cyclopentane-sesquiterpenoids (valerenic acid, acetoxyvalerenic acid, and valerenal) is confined to *V. officinalis* and permits its distinction from *V. edulis* and *V. wallichii* (*12*). The various subspecies of *V. officinalis* have different compositions of volatile oil and, for example, average bornyl acetate content varies from 35% in *V. officinalis* ssp. *pratensis* to 0.45% in *V. officinalis* ssp. *illyrica* (*12*).

A second important group of constituents (0.05–0.67% range) is a series of non-glycosidic bicyclic iridoid monoterpene epoxy-esters known as the valepotriates. The major valepotriates are valtrate and isovaltrate (which usually represent more than 90% of the valepotriate content). Smaller amounts of dihydrovaltrate, isovaleroxy-hydroxydihydrovaltrate, 1-acevaltrate or others are present (*8*, *12*). The valepotriates are rather unstable owing to their epoxide structure, and losses occur fairly rapidly on storage or processing, especially if the drug is not carefully dried. Principal degradation products are baldrinal, homobaldrinal, and valtroxal (*8*).



Dosage forms

Internal use as the expressed juice, tincture, extracts, and other galenical preparations (*8*, *22*). External use as a bath additive (*22*). Store in tightly closed containers, in a cool dry place, protected from light (*1–6*).

Medicinal uses

Uses supported by clinical data

As a mild sedative and sleep-promoting agent (*8*, *12*, *22–25*). The drug is often used as a milder alternative or a possible substitute for stronger synthetic sedatives, such as the benzodiazepines, in the treatment of states of nervous excitation and anxiety-induced sleep disturbances (*22–25*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a digestive aid, and an adjuvant in spasmolytic states of smooth muscle and gastrointestinal pains of nervous origin (*8*, *12*). When associated with papaverine, belladonna, and other spasmolytics, Radix Valerianae has been shown to be useful as an adjuvant in spastic states of smooth muscle such as spastic colitis (*8*).

Uses described in folk medicine, not supported by experimental or clinical data

To treat epilepsy, gum sores, headaches, nausea, sluggish liver, urinary tract disorders, vaginal yeast infections, and throat inflammations; and as an emmenagogue, antiperspirant, antidote to poisons, diuretic, anodyne, and a decoction for colds (*5*, *8*).

Pharmacology

Experimental pharmacology

The sedative activity of *V. officinalis* has been demonstrated both *in vitro* and *in vivo*. *In vitro* studies have demonstrated the binding of valerian extracts to GABA (γ-aminobutyric acid) receptors, adenosine receptors and the barbiturate and benzodiazepine receptors (*8*, *26*). Both hydroalcoholic and aqueous total extracts show affinity for the GABA-A receptors, but there is no clear correlation between any of the known chemical components isolated from Radix Valerianae and GABA-A binding activity (*8*). Aqueous extracts of the roots of *V. officinalis* inhibit re-uptake and stimulate the release of radiolabelled GABA in the synaptosomes isolated from rat brain cortex (*27*, *28*). This activity may increase the extracellular concentration of GABA in the synaptic cleft, and thereby enhance the biochemical and behavioural effects of GABA (*8*, *27*). Interestingly, GABA has been found in extracts of *V. officinalis* and appears to be responsible for this activity (*29*). The valtrates, and in particular dihydrovaltrate, also show some affinity for both the barbiturate receptors and the peripheral benzodiazepine receptors (*8*).

In vivo studies suggest that the sedative properties of the drug may be due to high concentrations of glutamine in the extracts (*29*). Glutamine is able to cross the blood–brain barrier, where it is taken up by nerve terminals and subse-

quently metabolized to GABA (*29*). The addition of exogenous glutamine stimulates GABA synthesis in synaptosomes and rat brain slices (*29*).

The spasmolytic activity of the valepotriates is principally due to valtrate or dihydrovaltrate (*30*). These agents act on centres of the central nervous system and through direct relaxation of smooth muscle (*31*), apparently by modulating Ca^{2+} entry into the cells or by binding to smooth muscle (*8*, *32*).

Clinical pharmacology

A number of clinical investigations have demonstrated the effectiveness of Radix Valerianae as a sleep aid and minor sedative (*8*, *22–25*). In a double-blind study, valerian (450 mg or 900 mg of an aqueous root extract) significantly decreased sleep latency as compared with a placebo (*23*). The higher dose of valerian did not further decrease sleep latency (*23*). Additional clinical studies have demonstrated that an aqueous extract of valerian root significantly increased sleep quality, in poor and irregular sleepers, but it had no effect on night awakenings or dream recall (*24*). The use of Radix Valerianae appears to increase slow-wave sleep in patients with low baseline values, without altering rapid eye movement (REM) sleep (*24*).

While extracts of the drug have been clearly shown to depress central nervous system activity, the identity of the active constituents still remains controversial. Neither the valepotriates, nor the sesquiterpenes valerenic acid and valeranone, nor the volatile oil alone can account for the overall sedative activity of the plant (*8*, *33*). It has been suggested that the baldrinals, degradation products of the valepotriates, may be responsible (*26*). Currently, it is still not known whether the activity of Radix Valerianae extracts resides in one compound, a group of compounds, or some unknown compound, or is due to a synergistic effect.

Contraindications

Radix Valerianae should not be used during pregnancy or lactation (*31*, *34*).

Warnings

No information available.

Precautions

General

May cause drowsiness. Those affected should not drive or operate machinery. Although no interaction between valerian and alcohol has been demonstrated clinically, as a precautionary measure patients should avoid consuming alcoholic beverages or other sedatives in conjunction with Radix Valerianae (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Some concern has been expressed over the cytotoxicity of the valepotriates. Cytotoxicity has been demonstrated *in vitro* but not *in vivo*, even in doses of 1350 mg/kg (*35*). Some of the valepotriates demonstrate alkylating activity *in vitro*. However, because the compounds decompose rapidly in the stored drug, there is no cause for concern (*35*). The valepotriates are also poorly absorbed and are rapidly metabolized to the baldrinals (*26*), which have better sedating effects. *In vitro*, the baldrinals are less toxic than the valepotriates, but *in vivo* they are more cytotoxic because they are more readily absorbed by the intestine. Baldrinals have been detected at levels up to 0.988 mg/dose in commercial preparations standardized with respect to the concentration of valepotriates and may be of cytotoxic concern (*36*).

Pregnancy: teratogenic effects

Prolonged oral administration of valepotriates did not produce any teratogenic effects (*8*, *37*).

Pregnancy: non-teratogenic effects

The safety of Radix Valerianae during pregnancy has not been established; therefore it should not be administered during pregnancy.

Nursing mothers

Excretion of Radix Valerianae into breast milk and its effects on the newborn infant have not been established; therefore it should not be administered during lactation.

Paediatric use

Radix Valerianae preparations should not be used for children less than 12 years of age without medical supervision (*34*).

Other precautions

No information on general precautions or drug interactions or drug and laboratory test interactions was found.

Adverse reactions

Minor side-effects have been associated with chronic use of Radix Valerianae and include headaches, excitability, uneasiness, and insomnia. Very large doses may cause bradycardia and arrhythmias, and decrease intestinal motility (*38*). The recommended first aid is gastric lavage, charcoal powder, and sodium sulfate (*38*). Doses up to 20 times the recommended therapeutic dose have been reported to cause only mild symptoms which resolved within 24 h (*38*). Four cases of liver damage have been associated with use of preparations containing

Radix Valerianae (*39*). However, in all cases the patients were taking a combination herbal product containing four different plant species and thus a causal relationship to the intake of valerian is extremely doubtful.

Posology

Dried root and rhizome, 2–3 g drug per cup by oral infusion, 1–5 times per day, up to a total of 10 g and preparations correspondingly (*6*, *22*). Tincture (1:5, 70% ethanol), 0.5–1 teaspoon (1–3 ml), once to several times a day. External use, 100 g drug for a full bath (*22*).

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Rhizoma Zingiberis

Definition

Rhizoma Zingiberis is the dried rhizome of *Zingiber officinale* Roscoe (*Zingiberaceae*) (*1–5*)

Synonyms

Amomum zingiber L. (*1, 6*), *Zingiber blancoi* Massk. (*6*).

Selected vernacular names

Ada, adrak, adu, African ginger, ajenjibre, ale, alea, allam, allamu, ardak, ardraka, ardrakam, ardrakamu, asunglasemtong, ata-le jinja, baojiang, beuing, chiang, citaraho, cochin ginger, common ginger, djae, gember, gengibre, gingembre, ginger, ginger root, gnji, gung, halia bara, halia, halija, hli, inchi, Ingberwurgel, inguere, inguru, Ingwer, jahe, Jamaica ginger, janzabeil, kallamu, kan chiang, kanga, kerati, khenseing, khiang, khing, khing-daeng, khing klaeng, khing phueak, khuong, kintoki, jion, konga, lahja, lei, luya, mangawizi, ngesnges, niamaku, oshoga, palana, palu, rimpang jahe, sa-e, sakanjabir, sge u-gser, shengiang, shenjing, shoga, shonkyoh, shokyo, shouhkyoh, tangawizi, wai, zanjabeel, zangabil ee-e-tar, zingabil urratab, zingibil, zingiberis rhizoma, zinjabil, zingiber, zinam (*1, 4, 6–13*).

Description

A perennial herb with a subterranean, digitately branched rhizome producing stems up to 1.50 m in height with linear lanceolate sheathing leaves (5–30 cm long and 8–20 mm wide) that are alternate, smooth and pale green. Flower stems shorter than leaf stems and bearing a few flowers, each surrounded by a thin bract and situated in axils of large, greenish yellow obtuse bracts, which are closely arranged at end of flower stem forming collectively an ovate-oblong spike. Each flower shows a superior tubular calyx, split part way down one side; an orange yellow corolla composed of a tube divided above into 3 linear-oblong, blunt lobes; 6 staminodes in 2 rows, the outer row of 3 inserted at mouth of corolla; the posterior 2, small, horn-like; the anterior petaloid, purple and spotted and divided into 3 rounded lobes; an inferior, 3-celled ovary with tufted stigma. Fruit a capsule with small arillate seeds (*1, 7, 8*).

Plant material of interest: dried rhizome

General appearance

Ginger occurs in horizontal, laterally flattened, irregularly branching pieces; 3–16 cm long, 3–4 cm wide, up to 2 cm thick; sometimes split longitudinally; pale yellowish buff or light brown externally, longitudinally striated, somewhat fibrous; branches known as "fingers" arise obliquely from the rhizomes, are flattish, obovate, short, about 1–3 cm long; fracture, short and starchy with projecting fibres. Internally, yellowish brown, showing a yellow endodermis separating the narrow cortex from the wide stele, and numerous scattered fibrovascular bundles, abundant scattered oleoresin cells with yellow contents and numerous larger greyish points, vascular bundles, scattered on the whole surface (*1–5*).

Organoleptic properties

Odour, characteristic aromatic; taste, pungent and aromatic (*1–5*); colour, internally pale yellow to brown (*1, 4*).

Microscopic characteristics

Cortex of isodiametric, thin-walled parenchyma cells contains abundant starch granules, each with a pointed hilum up to 50 μm long and 25 μm wide and 7 μm thick, and showing scattered secretion cells with suberized walls and yellowish brown oleoresinous content, and scattered bundles of the leaf-traces accompanied by fibres; endodermis, of pale brown, thin-walled cells with suberized radial walls; stele, with parenchymatous ground tissue, numerous yellow oleoresin secretion cells and numerous scattered, closed collateral vascular bundles with nonlignified, reticulate, scalariform, and spiral vessels, often accompanied by narrow cells; containing a dark brown pigment, and supported by thin-walled fibres with wide lumen, small oblique slit-like pits, and lignified middle lamella; some of the fibres are septate (*1, 3, 4*).

Powdered plant material

Powdered ginger is yellowish white to yellowish brown; characterized by numerous fragments of thin-walled parenchyma cells containing starch granules; fragments of thin-walled septate fibres with oblique slit-like pits; fragments of nonlignified scalariform, reticulate, and spiral vessels, often accompanied by dark pigment cells; oleoresin in fragments or droplets with oil cells and resin cells scattered in parenchyma; numerous starch granules, simple, flat, oval, oblong with terminal protuberance, in which the hilum is pointed, 5–60 μm usually 15–30 μm long, 5–40 μm (usually 18–25 μm) wide, 6–12 μm (usually 8–10 μm) thick with somewhat marked fine transverse striations (*1–4*).

Geographical distribution

The plant is probably native to south-east Asia and is cultivated in the tropical regions in both the eastern and western hemispheres. It is commercially grown

in Africa, China, India, and Jamaica; India is the world's largest producer (*1*, *4*, *6*, *7*, *10*, *14*).

General identity tests

Rhizoma Zingiberis is identified by its macroscopic and organoleptic characteristics, including its characteristic form, colour, pungent taste, and volatile oil content; and by microchemical tests *(1–5)*.

Purity tests

Microbiology

The test for *Salmonella* spp. in Rhizoma Zingiberis products should be negative. The maximum acceptable limits of other microorganisms are as follows (*15–17*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 2.0% (*1*). Powdered ginger is frequently adulterated with exhausted ginger (*8*).

Total ash

Not more than 6.0% (*2*, *3*).

Acid-insoluble ash

Not more than 2.0% (*5*).

Water-soluble extractive

Not less than 10% (*3*, *4*).

Alcohol-soluble extractive

Not less than 4.5% (*3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Rhizoma Zingiberis is not more than 0.05 mg/kg (*17*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residue (*18*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

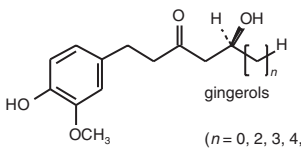
Chemical and moisture tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 2% v/w of volatile oil (*1*), as determined by the method described in WHO guidelines (*15*). Qualitative analysis by thin-layer chromatography (*1*); qualitative and quantitative gas chromatography and high-performance liquid chromatography analyses of ginger oils for gingerols, shogaols, α-zingiberene, β-bisabolene, β-sesquiphellandrene, and *ar*-curcumene (*19*).

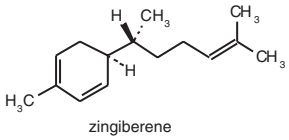
Major chemical constituents

The rhizome contains 1–4% essential oil and an oleoresin. The composition of the essential oil varies as a function of geographical origin, but the chief constituent sesquiterpene hydrocarbons (responsible for the aroma) seem to remain constant. These compounds include (−)-zingiberene, (+)-*ar*-curcumene, (−)-β-sesquiphellandrene, and β-bisabolene. Monoterpene aldehydes and alcohols are also present. The constituents responsible for the pungent taste of the drug and possibly part of its anti-emetic properties have been identified as 1-(3′-methoxy-4′-hydroxyphenyl)-5-hydroxyalkan-3-ones, known as [3–6]-, [8]-, [10]-, and [12]-gingerols (having a side-chain with 7–10, 12, 14, or 16 carbon atoms, respectively) and their corresponding dehydration products, which are known as shogaols (*1, 4, 6, 14, 19*). Representative structures of zingiberene, gingerols and shogaols are presented below.

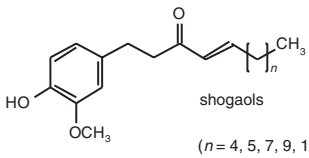


gingerols

(*n* = 0, 2, 3, 4, 5, 7, 9)



zingiberene



shogaols

(*n* = 4, 5, 7, 9, 10)

Dosage forms

Dried root powder, extract, tablets and tincture (*2*, *14*). Powdered ginger should be stored in well-closed containers (not plastic) which prevent access of moisture. Store protected from light in a cool, dry place (*4*, *5*).

Medicinal uses

Uses supported by clinical data

The prophylaxis of nausea and vomiting associated with motion sickness (*20*–*23*), postoperative nausea (*24*), pernicious vomiting in pregnancy (*25*), and seasickness (*26*, *27*).

Uses described in pharmacopoeias and in traditional systems of medicine

The treatment of dyspepsia, flatulence, colic, vomiting, diarrhoea, spasms, and other stomach complaints (*1*, *2*, *4*, *9*, *21*). Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite, as a narcotic antagonist (*1*, *2*, *4*, *6*, *11*, *12*, *21*), and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders (*9*, *11*, *12*, *28*).

Uses described in folk medicine, not supported by experimental or clinical data

To treat cataracts, toothache, insomnia, baldness, and haemorrhoids, and to increase longevity (*9*, *10*, *12*).

Pharmacology

Experimental pharmacology

Cholagogic activity

Intraduodenal administration of an acetone extract (mainly essential oils) of ginger root to rats increased bile secretion for 3 hours after dosing, while the aqueous extract was not active (*29*). The active constituents of the essential oil were identified as [6]- and [10]-gingerol (*29*).

Oral administration of an acetone extract of ginger (75 mg/kg), [6]-shogaol (2.5 mg/kg), or [6]-, [8]-, or [10]-gingerol enhanced gastrointestinal motility in mice (*30*), and the activity was comparable to or slightly weaker than that of metoclopramide (10 mg/kg) and domperidone (*30*). The [6]-, [8]-, or [10]-gingerols are reported to have antiserotoninergic activity, and it has been suggested that the effects of ginger on gastrointestinal motility may be due to this activity (*30*, *31*). The mode of administration appears to play a critical role in studies on gastrointestinal motility. For example, both [6]-gingerol and [6]-shogaol inhibited intestinal motility when administered intravenously but accentuated gastrointestinal motility after oral administration (*6*, *12*, *32*).

Antiemetic activity

The emetic action of the peripherally acting agent copper sulfate was inhibited in dogs given an intragastric dose of ginger extract (*33*), but emesis in pigeons treated with centrally acting emetics such as apomorphine and digitalis could not be inhibited by a ginger extract (*34*). These results suggest that ginger's antiemetic activity is peripheral and does not involve the central nervous system (*11*). The antiemetic action of ginger has been attributed to the combined action of zingerones and shogaols (*11*).

Anti-inflammatory activity

One of the mechanisms of inflammation is increased oxygenation of arachidonic acid, which is metabolized by cyclooxygenase and 5-lipoxygenase, leading to prostaglandin E_2 and leukotriene B_4, two potent mediators of inflammation (*28*). *In vitro* studies have demonstrated that a hot-water extract of ginger inhibited the activities of cyclooxygenase and lipoxygenase in the arachidonic acid cascade; thus its anti-inflammatory effects may be due to a decrease in the formation of prostaglandins and leukotrienes (*35*). The drug was also a potent inhibitor of thromboxane synthase, and raised prostacyclin levels without a concomitant rise in prostaglandins E_2 or $F_{2\alpha}$ (*36*). *In vivo* studies have shown that oral administration of ginger extracts decreased rat paw oedema (*37*, *38*). The potency of the extracts was comparable to that of acetylsalicylic acid. [6]-Shogaol inhibited carrageenin-induced paw oedema in rats by inhibiting cyclooxygenase activity (*39*). Recently, two labdane-type diterpene dialdehydes isolated from ginger extracts have been shown to be inhibitors of human 5-lipoxygenase *in vitro* (*40*).

Clinical pharmacology

Antinausea and antiemetic activities

Clinical studies have demonstrated that oral administration of powdered ginger root (940 mg) was more effective than dimenhydrinate (100 mg) in preventing the gastrointestinal symptoms of kinetosis (motion sickness) (*22*). The results of this study further suggested that ginger did not act centrally on the vomiting centre, but had a direct effect on the gastrointestinal tract through its aromatic, carminative, and absorbent properties, by increasing gastric motility and adsorption of toxins and acids (*22*).

In clinical double-blind randomized studies, the effect of powdered ginger root was tested as a prophylactic treatment for seasickness (*26*, *27*). The results of one study demonstrated that orally administered ginger was statistically better than a placebo in decreasing the incidence of vomiting and cold sweating 4 hours after ingestion (*27*). The other investigation compared the effects of seven over-the-counter and prescription antiemetic drugs on prevention of seasickness in 1489 subjects. This study concluded that ginger was as effective as the other antiemetic drugs tested (*26*).

At least eight clinical studies have assessed the effects of ginger root on the symptoms of motion sickness. Four of these investigations showed that orally administered ginger root was effective for prophylactic therapy of nausea and vomiting. The other three studies showed that ginger was no more effective than a placebo in treating motion sickness (*23*, *41*, *42*). The conflicting results appear to be a function of the focus of these studies. Clinical studies that focused on the gastrointestinal reactions involved in motion sickness recorded better responses than those studies that concentrated primarily on responses involving the central nervous system.

The hypothesis that an increase in gastric emptying may be involved in the antiemetic effects of ginger has recently come under scrutiny. Two clinical studies demonstrated that oral doses of ginger did not affect the gastric emptying rate, as measured by sequential gastric scintigraphy (*43*) or the paracetamol absorption technique (*44*).

In a double-blind, randomized, cross-over trial, oral administration of powdered ginger (250 mg, 4 times daily) effectively treated pernicious vomiting in pregnancy (*25*). Both the degree of nausea and the number of vomiting attacks were significantly reduced (*25*). Furthermore, in a prospective, randomized, double-blind study, there were statistically significantly fewer cases of postoperative nausea and vomiting in 60 patients receiving ginger compared to a placebo (*24*). The effect of ginger on postoperative nausea and vomiting was reported to be as good as or better than that of metoclopramide (*24*, *45*). In contrast, another double-blind randomized study concluded that orally administered ginger BP (prepared according to the British Pharmacopoeia) was ineffective in reducing the incidence of postoperative nausea and vomiting (*46*).

Anti-inflammatory activity

One study in China reported that 113 patients with rheumatic pain and chronic lower back pain, injected with a 5–10% ginger extract into the painful points or reaction nodules, experienced full or partial relief of pain, decrease in joint swelling, and improvement or recovery in joint function (*11*). Oral administration of powdered ginger to patients with rheumatism and musculoskeletal disorders has been reported to provide varying degrees of relief from pain and swelling (*28*).

Contraindications

No information available.

Warnings

No information available.

Precautions

General

Patients taking anticoagulant drugs or those with blood coagulation disorders should consult their physician prior to self-medication with ginger. Patients with gallstones should consult their physician before using ginger preparations (*21*).

Drug interactions

Ginger may affect bleeding times and immunological parameters owing to its ability to inhibit thromboxane synthase and to act as a prostacyclin agonist (*47, 48*). However, a randomized, double-blind study of the effects of dried ginger (2 g daily, orally for 14 days) on platelet function showed no differences in bleeding times in patients receiving ginger or a placebo (*49, 50*). Large doses (12–14 g) of ginger may enhance the hypothrombinaemic effects of anticoagulant therapy, but the clinical significance has yet to be evaluated.

Carcinogenesis, mutagenesis, impairment of fertility

The mutagenicity of ginger extracts is a controversial subject. A hot-water extract of ginger was reported to be mutagenic in B291I cells and *Salmonella typhimurium* strain TA 100, but not in strain TA 98 (*51*). A number of constituents of fresh ginger have been identified as mutagens. Both [6]-gingerol and shogaols have been determined to be mutagenic in a *Salmonella*/microsome assay (*52*), and increased mutagenesis was observed in an Hs30 strain of *Escherichia coli* treated with [6]-gingerol (*53*). However, the mutagenicity of [6]-gingerol and shogaols was suppressed in the presence of various concentrations of zingerone, an antimutagenic constituent of ginger (*52*). Furthermore, ginger juice was reported to be antimutagenic and suppressed the spontaneous mutations induced by [6]-gingerol, except in cases where the mutagenic chemicals 2-(2-furyl)-3-(5-nitro-2-furyl)acryl amide and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine were added to [6]-gingerol (*54*). Other investigators have also reported that ginger juice is antimutagenic (*54, 55*).

Pregnancy: teratogenic effects

In a double-blind randomized cross-over clinical trial, ginger (250 mg by mouth, 4 times daily) effectively treated pernicious vomiting in pregnancy (*25*). No teratogenic aberrations were observed in infants born during this study, and all newborn babies had Apgar scores of 9 or 10 after 5 minutes (*25*).

Paediatric use

Not recommended for children less than 6 years of age.

Other precautions

No information available concerning drug and laboratory test interactions, or non-teratogenic effects on pregnancy or nursing mothers.

Adverse reactions

Contact dermatitis of the finger tips has been reported in sensitive patients (*56*).

Posology

For motion sickness in adults and children more than 6 years: 0.5 g, 2–4 times daily. Dyspepsia, 2–4 g daily, as powdered plant material or extracts (*21*).

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Annex

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WHO monographs on selected medicinal plants

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Introduction

Role of the *WHO monographs on selected medicinal plants*

The first volume of the *WHO monographs on selected medicinal plants*, containing 28 monographs, was published in 1999. It is gratifying that the importance of the monographs is already being recognized. For example, the European Commission has recommended volume 1 to its Member States as an authoritative reference on the quality, safety and efficacy of medicinal plants. The Canadian Government has also made a similar recommendation. Furthermore, as hoped, some of WHO's Member States, such as Benin, Mexico, South Africa and Viet Nam, have developed their own monographs based on the format of the WHO monographs.

The monographs are not only a valuable scientific reference for health authorities, scientists and pharmacists, but will also be of interest to the general public. There can be little doubt that the WHO monographs will continue to play an important role in promoting the proper use of medicinal plants throughout the world.

Preparation of monographs for volume 2

At the eighth International Conference on Drug Regulatory Authorities (ICDRA) held in Manama, Bahrain, in 1996, WHO reported the completion of volume 1 of the WHO monographs. Member States requested WHO to continue to develop additional monographs. As a consequence, preparation of the second volume began in 1997.

During the preparation, the number of experts involved, in addition to members of WHO's Expert Advisory Panel on Traditional Medicine, significantly increased compared to that for volume 1. Similarly, the number of national drug regulatory authorities who participated in the preparation also greatly increased. This global network of active collaborators facilitated wider access to the scientific references and information, thus increasing both the quality and quantity of the monographs. These combined efforts greatly improved the efficiency of the preparation. As for volume 1, the monographs were drafted by the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, United States of America.

The Second WHO Consultation on Selected Medicinal Plants was held in Ravello-Salerno, Italy, in March 1999 to review and finalize the draft monographs. Twenty experts and drug regulatory authorities from WHO Member

States participated (see Annex 1). Following extensive discussion, 30 of 31 draft monographs were approved for volume 2. At the subsequent ninth ICDRA in Berlin, Germany in April 1999, the 30 draft monographs were presented, and Member States requested WHO to publish them as soon as possible.

Purpose and content of the monographs

The purpose of the monographs was clearly explained in the introduction to volume 1, and it is unnecessary to repeat it here. However, it is important to emphasize that the word "monograph", as appears in the title, is used as a technical term only. These monographs are not intended to be official pharmacopoeial monographs.

It should also be stressed that this publication is not intended to replace official compendia such as pharmacopoeias, formularies or legislative documents. Furthermore, the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of facilitating information exchange.

A description of selected sections of the monographs is given in the *General technical notices*. For easy reference, two cumulative indexes are also provided as annexes. Annex 2 lists the monographs in alphabetical order of the plant name, while Annex 3 is according to the plant material of interest.

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General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO's Member States; to provide models to assist WHO's Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO's Member States.

The format used for volume 2 essentially follows that of volume 1. However, to keep relevant sections together, *Geographical distribution* now precedes *Description*; and *Dosage forms* appears before *Posology*.

The *Definition* describes the identity of the plant material of interest and the Latin binomial name of the source plant, the binomial name being the most important criterion in quality assurance of the crude drug. Latin pharmacopoeial synonyms and vernacular names, listed in the sections *Synonyms* and *Selected vernacular names*, respectively, are those names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the *International rules of nomenclature*.

The vernacular names listed are a selection of names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. The lists are not complete, but reflect the names found at the time of preparation in official monographs, reference books and the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, USA).

A detailed botanical description (in *Description*) is intended for quality assurance at the stages of production and collection of the source plant, whereas the detailed description of the specific plant part used (the crude drug)—in *Plant material of interest*—is for quality assurance at the manufacturing and commercial stages. *Geographical distribution* is not normally found in official compendia, but it is included here to provide additional quality assurance information.

General identity tests, *Purity tests* and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with requirements of the respective national health authorities.

Each medicinal plant and crude drug contains active or major chemical constituents with a characteristic profile that can be used for chemical quality

control and quality assurance. These constituents are described in the section *Major chemical constituents*.

Descriptions included in the section on *Medicinal uses* should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange. Medicinal uses are categorized as uses supported by clinical data; uses described in pharmacopoeias and in traditional systems of medicine; and uses described in folk medicine, not yet supported by experimental or clinical data.

The first category includes medicinal indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. The clinical trials may have been controlled, randomized, double-blind studies, trials without controls, cohort studies, or well-documented observations of therapeutic applications.

The second category includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or national monographs. Well-established uses having a plausible pharmacological basis and supported by older studies that clearly need to be repeated are also included. The references cited provide additional information useful in evaluating specific herbal preparations. The uses described should be reviewed by local experts and health workers for their applicability in the local situation.

The third category refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. The appropriateness of these uses could not be assessed, owing to a lack of scientific data to support the claims. The possible uses of these remedies must be carefully considered in the light of therapeutic alternatives.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Abbreviated details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included to avoid confusion.

The details included in the section on *References* have been checked against the original sources wherever possible. However, in some cases, details are missing as the original sources were not available. For non-English language references, the title is given in the original language, except in cases where an English summary is available.

Radix Althaeae

Definition

Radix Althaeae consists of the dried roots of *Althaea officinalis* L. (Malvaceae) (*1–4*).

Synonym

Malva officinalis L. (*5*).

Selected vernacular names

Altea, altee, althea, bardul khatmi, benefischi, bismalva-hibiscus, blanca malva, bon visclo, bourdon de St Jacques, Eibisch, Eibischwurzel, erva molle, guimauve, Heilwurz, hobbiza, Ibischwurz, khairi, khatmi, korzén prawó-slazu, marshmallow, marshmallow root, malvaccioniu, malvavisco, marmo-lone, molotta, Moorish mallow, orvosiziliz gyökér, racine d'althée, racine de guimauve, Sammetpappel, sauvage, Schleimwurzel, suzmool, sweet weed, white mallow, wymote (3, *6–8*).

Geographical distribution

Indigenous to western Asia and Europe, and is naturalized in the United States of America (*9*, *10*). Roots are obtained from commercially cultivated plants that are at least 2 years old and harvested in the autumn (*6*, *10*).

Description

A perennial herb with erect, woody stems, 60–120 cm high. Leaves alternate, ovate to slightly cordate, serrate, velvety, large, occasionally 3-lobed. Flowers pale pink, axillary, the calyx of each surrounded by a 6–9 cleft involucre. Fruit a set of cocci united into a ring (*11*).

Plant material of interest: dried roots

General appearance

Cylindrical or tapering, slightly twisted roots, up to 2 cm thick, with deep longitudinal furrows. Outer surface greyish-brown, bearing numerous rootlet scars. Fracture externally fibrous, internally rugged and granular; section shows

a thick, whitish bark with brownish periderm, separated by a well-marked, brownish cambium from the white xylem; stratified structure of the bark and radiate structure of xylem become more distinct when moist. Peeled root has greyish-white finely fibrous outer surface; cork and external cortical parenchyma absent (*2*).

Organoleptic properties

Odour: faint, aromatic; taste: mucilaginous (*1*).

Microscopic characteristics

Phloem with numerous long, thin-walled, non-lignified fibres arranged in tangential groups alternating with groups of sieve tissue, with a ground tissue of thin-walled parenchyma; xylem containing reticulate or scalariform thickening and bordered pits accompanied by lignified tracheids, a small amount of lignified parenchyma and occasional small groups of fibres with only the middle lamella lignified; xylem and phloem transversed by numerous non-lignified medullary rays, mostly uniseriate; majority of parenchyma cells of the phloem and medullary rays contain abundant small starch grains which are mostly simple, spherical to ovoid, occasionally 2–3 compound, with a well-marked circular or slit-shaped hilum; some of these parenchyma cells contain cluster crystals of calcium oxalate 20–40 μm in diameter, while others exist as idioblasts containing mucilage (*1*).

Powdered plant material

Brownish-grey (unpeeled root) or whitish (peeled root). Fragments of colourless, mainly unlignified, thick-walled fibres with pointed or split ends; fragments of reticulate or scalariform thickening and bordered pits; cluster crystals of calcium oxalate about 20–35 μm, mostly 25–30 μm, in diameter; parenchyma cells containing mucilage; fragments of cork with thin-walled, tabular cells in the powdered material from the unpeeled root. Numerous starch grains, 3–25 μm in diameter, with occasionally a longitudinal hilum; starch grains mostly simple, a few being 2–4 compound (*2*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*).

Purity tests

Microbiology

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 2% of brown, deteriorated drug and not more than 2% of cork in the peeled root (*2*).

Total ash

Not more than 6% in the peeled root and not more than 8% in the unpeeled root (*2*).

Acid-insoluble ash

Not more than 3% in the peeled root (*1*).

Water-soluble extractive

Not less than 22% (*1*).

Loss on drying

Not more than 12% (*2*).

Swelling index

Not less than 10 (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Not less than 10% total mucilage in the peeled root as determined by gravimetric analysis (*14*).

Major chemical constituents

The mucilage content ranges from 10 to 20% and consists of a mixture of acidic galacturonorhamnans, neutral glucans and neutral arabinogalactans (*6*, *8*, *9*, *15–17*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and pharyngeal mucosa and as an emollient for wounds and dry skin (*8*, *18–23*). Also used in cough mixtures to mask the bitter or pungent taste of other drugs (*16*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, cystitis, dysentery and irritations of the gastric mucosa (*7*).

Pharmacology

Experimental pharmacology

The demulcent effects of Radix Althaeae are due to its high content of polysaccharide hydrocolloids, which form a protective coating on the oral and pharyngeal mucosa, soothing local irritation and inflammation (*24*).

Anti-inflammatory activity

A polysaccharide fraction (500 µg/ml) isolated from a root extract had anti-complement activity in human serum in vitro (*25*). Aqueous extracts of the roots stimulated phagocytosis, and the release of oxygen radicals and leukotrienes from human neutrophils in vitro (*26*). The aqueous extract also induced the release of cytokines, interleukin-6 and tumour necrosis factor from human monocytes in vitro, thereby exhibiting anti-inflammatory and immunostimulant activity (*26*). Intraperitoneal administration of isolated mucilage polysaccharides to mice (10 mg/kg body weight) induced a 2.2-fold increase in the phagocytic activity of macrophages as measured by the colloidal carbon clearance test (*27*). However, intragastric administration of an 80% ethanol extract of the roots to rats (100 mg/kg body weight) did not inhibit carrageenan-induced footpad oedema (*28*).

Weak inhibition (17%) of mucociliary transport in isolated, ciliated epithelium of the frog oesophagus was demonstrated after treatment of the isolated tissues with 200 µl of an aqueous root macerate (6.4 g/140 ml) (*29*).

Antitussive activity

Intragastric administration of a polysaccharide fraction, isolated from an aqueous root extract, to cats (50 mg/kg body weight) suppressed the intensity and the frequency of coughs induced by mechanical irritation of laryngopharyngeal and tracheobronchial mucosa (*30*). The antitussive activity of this polysaccharide fraction (50 mg/kg body weight) was as effective as Syrupus Althaeae (1.0 g/kg body weight), and more effective than prenoxdiazine (30 mg/kg body weight) (*30*).

Clinical pharmacology

None.

Contraindications

No information available.

Warnings

No information available.

Precautions

Drug interactions

Simultaneous administration of Radix Althaeae may delay the absorption of other drugs (*8*).

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Radix Althaeae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

No information available.

Dosage forms

Peeled or unpeeled, broken, chopped or powdered crude drug (*1*, *2*) and galenical preparations thereof. Store in a well-closed container, protected from light (*2*).

Posology

(Unless otherwise indicated)

For dry cough, oral or pharyngeal irritation: 0.5–3.0 g of crude drug as an aqueous, cold macerate (*14*, *19*, *20*, *31*) or 2–8 ml of syrup (*20*, *22*, *32*), which may be repeated up to a daily dose of 15 g of crude drug. For gastric irritation: 3–5 g of crude drug as an aqueous, cold macerate up to three times daily (*19*, *20*, *31*).

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Herba Andrographidis

Definition

Herba Andrographidis consists of the dried aerial parts of *Andrographis paniculata* (Burm. f.) Nees (Acanthaceae) (*1*–*3*).

Synonyms

Justicia latebrosa Russ., *J. paniculata* Burm. f., *J. stricta* Lam. ex Steud. (*3*, *4*).

Selected vernacular names

Akar cerita bidara, alui, Andrographidis Kraut, bidara, bhoonimba, bhuinimo, bhulimb, bhuninba, charayeta, charayetha, charita, cheranta, cherota, chiraita, chiretta, chuan-hsin-lien, chuān-xīn-lián, công công, faathalaaichon, fathalaai, fathalaichon, fathalaijone, halviva, herba sambiloto, hinbinkohomba, I-chien-hsi, kalafath, kalmegh, kan-jang, kariyat, khee-pang-hee, king of bitters, kiriathu, kirta, kiryata, kiryato, lanhelian, mahatikta, mahatita, naelavemu, nay-nahudandi, nelavemu, quasab-uz-zarirah, rice bitters, sambilata, sambiloto, senshinren, sinta, xuyên tâm liên, yaa kannguu yijianxi (*1*, *2*, *5*–*11*).

Geographical distribution

Widely found and cultivated in tropical and subtropical Asia, south-east Asia and India (*6*, *8*, *10*).

Description

A herbaceous annual, erect, up to 1 m high; stem acutely quadrangular, much branched. Leaves simple, opposite, lanceolate, glabrous, 2–12 cm long, 1–3 cm wide; apex acute; margin entire, slightly undulate, upper leaves often bractiform; petiole short. Inflorescence patent, terminal and axillary in panicle, 10–30 mm long; bract small; pedicel short. Calyx 5-particle, small, linear. Corolla tube narrow, about 6 mm long; limb longer than the tube, bilabiate; upper lip oblong, white with a yellowish top; lower lip broadly cuneate, 3-lobed, white with violet markings. Stamens 2, inserted in the throat and far exserted; anther basally bearded. Superior ovary, 2-celled; style far exserted. Capsule erect, linear-oblong, 1–2 cm long and 2–5 mm wide, compressed, longitudinally furrowed on broad faces, acute at both ends, thinly glandular-hairy. Seeds small, subquadrate (*1*–*3*, *5*, *10*).

Plant material of interest: dried aerial parts

General appearance

Mixture of broken, crisp, mainly dark green lanceolate leaves and quadrangular stems; capsule fruit and small flowers occasionally found (*1*, *3*). Stem texture fragile, easily broken; leaves simple, petiole short or nearly sessile, lanceolate or ovate-lanceolate, with acuminate apex and cuneate-decurrent base, lamina crumpled and easily broken (*2*).

Organoleptic properties

Odour: slight, characteristic; taste: intensely bitter (*1–3*, *9*).

Microscopic characteristics

Leaf upper epidermis: stomata absent, glandular trichomes present, unicellular and multicellular trichomes rare, cystoliths fairly large; lithocysts large (27–30 µm thick, 96–210 µm long and up to 49 µm wide); columnar palisade cells; collenchyma in midrib beneath epidermis; parenchyma cells spongy; vascular bundles of lignified xylem in the upper part and lignified phloem in the lower part; spiral, scalariform and reticulate vessels. Leaf lower epidermis: a layer of wavy-walled cells; stomata diacytic; trichomes up to 36 µm in diameter and 180 µm long, and cystoliths present. Stem: epidermis has glandular and non-glandular trichomes. Collenchyma dense at the corners of stems; parenchyma contains chloroplastids. Endodermis composed of a layer of thick-walled cells. Wood with spiral, scalariform and pitted xylem vessels; pith composed of large parenchyma cells. Small acicular crystals of calcium oxalate occur in the pith and cortical cells of stem and leaf (*1–3*, *8*).

Powdered plant material

Leaf fragments in surface view show upper epidermis with underlying palisade and cystoliths, lower epidermis with underlying palisade cells with stomata, cystoliths and glandular trichomes. Leaf fragments in sectional view show upper epidermis with palisade cells, spongy parenchyma cells, vascular bundles; and lower epidermis with bundles of xylem associated with fibres; fragments of spiral, scalariform, reticulate and pitted vessels; fragments of epidermal cells from midrib; fragments of parenchyma cells in transverse and longitudinal sections. Bundles of fibres. Fragments of epidermal cells from stem with stomata, cystoliths and glandular trichomes. Scattered cystoliths; scattered unicellular and multicellular trichomes, mostly from epidermal cells in fruit walls; scattered glandular trichomes from bundles of fibres in fruit wall; scattered pollen grains (*1*).

General identity tests

Macroscopic and microscopic examinations, chemical tests, and thin-layer chromatography for the presence of diterpene lactones (*1–3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Chemical

Not less than 6% of total diterpene lactones, calculated as andrographolide (*1*, *3*).

Foreign organic matter

Not more than 2% (*1*, *3*).

Acid-insoluble ash

Not more than 2% (*1*, *3*).

Water-soluble extractive

Not less than 18% (*1*, *3*).

Alcohol-soluble extractive

Not less than 13% using 85% ethanol (*1*, *3*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

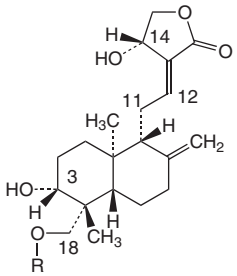
Total ash test to be established in accordance with national requirements.

Chemical assays

Chemical and thin-layer chromatography methods are used for qualitative analysis of andrographolide diterpene lactones (*1*, *2*). Titrimetric (*1*) and high-performance liquid chromatography (*15*) methods are available for quantitative analysis of total diterpene lactones.

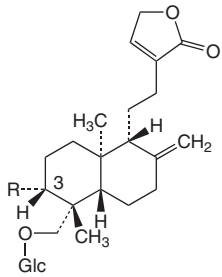
Major chemical constituents

The major constituents are diterpene lactones (free and in glycosidic forms) including andrographolide, deoxyandrographolide, 11,12-didehydro-14-deoxyandrographolide, neoandrographolide, andrographiside, deoxyandrographiside and andropanoside (*1*, *3*, *6*, *7*, *9*, *16*). The structures of andrographolide and related diterpene lactones are presented below.



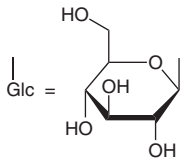
andrographolide R = H

andrographiside R = Glc



neoandrographolide R = H

andropanoside R = OH



β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

Prophylaxis and symptomatic treatment of upper respiratory infections, such as the common cold and uncomplicated sinusitis (*17–19*), bronchitis (*6*, *9*) and pharyngotonsillitis (*20*), lower urinary tract infections (*21*) and acute diarrhoea (*22*, *23*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of bacillary dysentery, bronchitis, carbuncles, colitis, coughs, dyspepsia, fevers, hepatitis, malaria, mouth ulcers, sores, tuberculosis and venomous snake bites (*1*, *2*, *6*, *7*, *10*, *16*, *24–27*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of colic, otitis media, vaginitis, pelvic inflammatory disease, chickenpox, eczema and burns (*6*, *7*).

Pharmacology
Experimental pharmacology
Antibacterial activity

An ethanol extract of the leaves inhibited the growth in vitro of *Escherichia coli* and *Staphylococcus aureus* (*28*). A 50% methanol extract of the leaves inhibited growth in vitro of *Proteus vulgaris* (*29*). However, no in vitro antibacterial activity was observed when dried powder from the aerial parts was tested against *E. coli*, *Staphylococcus aureus*, *Salmonella typhi* or *Shigella* species (*30*).

Anti-human immunodeficiency virus (HIV) activity

Aqueous extracts of the leaves inhibited HIV-1 infection and replication in the lymphoid cell line MOLT-4 (*31*). A hot aqueous extract of the aerial parts reduced the percentage of HIV antigen-positive H9 cells (*32*). Dehydroandrographolide inhibited HIV-1 and HIV-1 (UCD123) infection of H9 cells at 1.6 µg/ml and 50 µg/ml, respectively, and also inhibited HIV-1 infection of human lymphocytes at 50 µg/ml (*33*). A methanol extract of the leaves suppressed syncytia formation in co-cultures of uninfected and HIV-1-infected MOLT cells (median effective dose [ED_{50}] 70 µg/ml) (*34*).

Immunostimulatory activity

Intragastric administration of an ethanol extract of the aerial parts (25 mg/kg body weight) or purified andrographolides (1 mg/kg body weight) to mice stimulated antibody production and the delayed-type hypersensitivity response to sheep red blood cells (*35*). The extract also stimulated a non-specific immune response in mice, measured by macrophage migration index, phagocytosis of [^{14}C]leucine-labelled *E. coli*, and proliferation of splenic lymphocytes (*35*). The extract was more effective than either andrographolide or neoandrographolide alone, suggesting that other constituents may be involved in the immunostimulant response (*35*).

Antipyretic activity

Intragastric administration of an ethanol extract of the aerial parts (500 mg/kg body weight) to rats decreased yeast-induced pyrexia (*36*). The extract was reported to be as effective as 200 mg/kg body weight of aspirin, and no toxicity was observed at doses up to 600 mg/kg body weight (*36*). Intragastric administration of andrographolide (100 mg/kg body weight) to mice decreased brewer's yeast-induced pyrexia (*37*). Intragastric administration of deoxyandrographolide, andrographolide, neoandrographolide or 11,12-didehydro-14-deoxyandrographolide (100 mg/kg body weight) to mice, rats or rabbits reduced pyrexia induced by 2,4-dinitrophenol or endotoxins (*6*, *38*).

Antidiarrhoeal activity

Herba Andrographidis has antidiarrhoeal activity in situ (*39*, *40*). An ethanol, chloroform or 1-butanol extract of the aerial parts (300 mg/ml) inhibited the

E. coli enterotoxin-induced secretory response—which causes a diarrhoeal syndrome—in the rabbit and guinea-pig ileal loop assay (*39*, *40*). However, an aqueous extract of the aerial parts was not active (*40*). The constituent diterpene lactones, andrographolide and neoandrographolide, exhibited potent antisecretory activity in vivo against *E. coli* enterotoxin-induced diarrhoea (*40*). Andrographolide (1 mg per loop) was as active as loperamide when tested against heat-labile *E. coli* enterotoxin-induced diarrhoea and more effective than loperamide when tested against heat-stable *E. coli* enterotoxin-induced diarrhoea (*40*). Neoandrographolide (1 mg per loop) was as effective as loperamide when tested against heat-labile *E. coli* enterotoxin-induced diarrhoea and slightly less active than loperamide when tested against heat-stable *E. coli* enterotoxin-induced diarrhoea (*40*). The mechanism of action involves inhibition of the intestinal secretory response induced by heat-labile *E. coli* enterotoxins, which are known to act through the stimulation of adenylate cyclase, and by inhibition of the secretion induced by heat-stable *E. coli* enterotoxins, which act through the activation of guanylate cyclase (*39*). Incubation of murine macrophages with andrographolide (1–50 µmol/l) inhibited bacterial endotoxin-induced nitrite accumulation in a concentration- and time-dependent manner. Western blot analysis demonstrated that andrographolide inhibited the expression of an inducible isoform of nitric oxide synthase linked to endotoxin-induced circulatory shock (*41*).

Anti-inflammatory activity

Intragastric administration of deoxyandrographolide, andrographolide, neoandrographolide or 11,12-didehydrodeoxyandrographolide to mice inhibited the increase in cutaneous or peritoneal capillary permeability induced by xylene or acetic acid, and reduced acute exudation in Selye granulocysts treated with croton oil. 11,12-Didehydrodeoxyandrographolide had the most potent anti-inflammatory activity in vivo (*6*).

Antimalarial activity

A 50% ethanol extract of the aerial parts inhibited the growth of *Plasmodium berghei* both in vitro (100 mg/ml) and in mice after intragastric administration (1 g/kg body weight) (*42*). Intragastric administration of a 1-butanol, chloroform or ethanol–water extract of the aerial parts to *Mastomys natalensis* inhibited the growth of *P. berghei* at doses of 1–2 g/kg body weight (*43*). Andrographolide (5 mg/kg body weight) and neoandrographolide (2.5 mg/kg body weight) were also effective when administered by gastric lavage (*43*).

Antivenom activity

Intraperitoneal injection of an ethanol extract of the aerial parts (25 g/kg body weight) to mice poisoned with cobra venom markedly delayed the occurrence of respiratory failure and death (*6*, *44*). The same extract induced contractions in guinea-pig ileum at concentrations of 2 mg/ml. The contractions were

enhanced by physostigmine and blocked by atropine, but were unchanged by antihistamines (*44*). These data suggest that extracts of the aerial parts do not modify the activity of the nicotinic receptors but produce significant muscarinic activity, which accounts for its antivenom effects (*6*, *44*).

Antihepatotoxic activity

The aerial parts and their constituent andrographolides have antihepatotoxic activity in vitro and in vivo (*45–54*). Intraperitoneal administration of a methanol extract of the aerial parts (861.3 mg/kg body weight) to mice reduced hepatotoxicity induced by carbon tetrachloride (CCl_4), and reversed CCl_4-induced histopathological changes in the liver (*52*). Intraperitoneal administration of andrographolide (100 mg/kg body weight) to mice inhibited the CCl_4-induced increase in the activity of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin and hepatic triglycerides (*52*). Intraperitoneal administration of a methanol extract of the aerial parts (500 mg/kg body weight) to rats also suppressed the CCl_4-induced increase in the activity of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase and bilirubin (*51*). Intragastric administration of an aqueous extract of the aerial parts (500 mg/kg body weight) to ethanol-treated rats decreased the activity of serum transaminases and suppressed histopathological changes in the liver (*49*). Andrographolide, the major antihepatotoxic component of the plant, exerted a pronounced protective effect in rats against hepatotoxicity induced by CCl_4 (*47*), D-galactosamine (*54*), paracetamol (*48*) and ethanol (*49*). Andrographolide was more effective than silymarin, the standard hepatoprotective agent (*47*, *48*).

Clinical pharmacology

The common cold

Herba Andrographidis has been used clinically for symptomatic treatment of the common cold and uncomplicated sinusitis, pharyngotonsillitis, pneumonia and bronchitis (*6*, *17*, *18*, *20*). A placebo-controlled, double-blind clinical trial assessed the efficacy of a standardized extract of the aerial parts (containing 4% andrographolides) for treatment of the common cold in 61 adult patients. A significant reduction ($P < 0.0001$) in clinical symptoms such as sore throat, tiredness, muscular ache and malaise was observed on day 4 in the group receiving 1200 mg extract daily, as compared with the placebo group. No adverse reactions were reported in either group (*17*).

A randomized, placebo-controlled, double-blind pilot trial was conducted to evaluate the efficacy of a standardized extract of the aerial parts (containing 4% andrographolides) on the initial symptoms of the common cold and uncomplicated sinusitis. Fifty adult patients received either 1020 mg extract or a placebo daily for 5 days. The results demonstrated that patients in the treated group took less sick leave than those in the placebo group (0.21 day compared to 0.96 day). Furthermore, 68% of treated patients felt totally recovered, as

compared with 36% of the placebo group. Also 55% of the treated patients thought that the course of illness was much easier than normal, as compared with 19% of the placebo group (*18*).

A randomized, placebo-controlled, double-blind study evaluated a standardized extract of the aerial parts (containing 4% andrographolides) in the prophylaxis of the common cold in 107 schoolchildren during the winter season. The children received either 200 mg extract or a placebo daily for 3 months and were evaluated weekly by a physician. There was no difference in the occurrence of colds between the two groups during the first 2 months of treatment. However, after the third month of treatment, there was a significant difference ($P < 0.05$) in the occurrence of the common cold in the treated group (30%) as compared with the placebo group (62%) (*19*).

A randomized, double-blind comparison study of 152 adult patients with pharyngotonsillitis evaluated the efficacy of powdered aerial parts (6 g daily) and paracetamol (1 capsule of 325 mg as needed) for improving symptomatology. Baseline evaluation showed no significant difference between the two groups. The crude drug was as effective as paracetamol in reducing the incidence of sore throat and fever after 3 days of treatment (*20*). In a study without controls, treatment of patients with a standardized extract of *A. paniculata* (containing 4% andrographolides) reduced the incidence of fever associated with the common cold. The body temperature of patients treated with the extract was lowered in less than 48 hours after treatment (*55*). This finding was confirmed in a later study (*17*).

Urinary infections

A clinical trial compared the efficacy of Herba Andrographidis, co-trimoxazole (sulfamethoxazole + trimethoprim) and norfloxacin in the prevention of urinary tract infections after extracorporeal shock wave lithotripsy. Patients received a 5-day course of either Herba Andrographidis (4 tablets of 250 mg, three times daily) or co-trimoxazole (2 tablets of 25 mg, twice daily) or norfloxacin (1 tablet of 200 mg, twice daily). After 1 month of treatment, urinalysis results of 100 patients demonstrated that pyuria, haematuria and proteinuria were reduced in all treatment groups, and there was no significant difference between the three treatments (*21*).

Dysentery

The aerial parts have been used for the treatment of acute bacillary dysentery and enteritis (*2*, *6*, *22*, *23*). In clinical studies, the combination of andrographolide and neoandrographolide was reported to be more effective than either furazolidine or chloramphenicol in the treatment of bacillary dysentery (*6*). A randomized, double-blind clinical study of 200 patients compared the efficacy of the powdered aerial parts with tetracycline in the treatment of acute diarrhoea and bacillary dysentery (*22*, *23*). Patients received capsules of either the aerial parts or tetracycline (both 500 mg, four times daily) for 3 days. Compared with tetracycline, the aerial parts decreased the diarrhoea (both the fre-

quency and amount of discharge) (*22*). Furthermore, the aerial parts were more effective in treating diarrhoea resulting from shigellosis than from cholera (*22*).

Infectious hepatitis

Administration of a decoction of the aerial parts to patients with infectious hepatitis was reported to provide symptomatic relief (*24*).

Contraindications

Herba Andrographidis should not be used during pregnancy or lactation. Herba Andrographidis is contraindicated in cases of known allergy to plants of the Acanthaceae family.

Warnings

Due to potential anaphylactic reactions, crude extracts of Herba Andrographidis should not be injected (*6*, *56*).

Precautions

Drug interactions

Extracts of Herba Andrographidis may have a synergistic effect with isoniazid (*6*).

Carcinogenesis, mutagenesis, impairment of fertility

Herba Andrographidis extracts are not mutagenic in vitro (*57*) and have anti-mutagenic activity (*58*). A standardized extract of *A. paniculata* did not produce reproductive toxicity in male rats after 60 days of intragastric administration of 20–1000 mg/kg body weight daily (*59*).

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

In vivo studies in mice and rabbits suggest that Herba Andrographidis may have abortifacient activity (*6*, *60*). Conversely, no interruption of pregnancy, fetal resorption or decrease in the number of live offspring was observed in pregnant rats after intragastric administration of an extract of the aerial parts at 2 g/kg body weight during the first 9 days of gestation (*61*). Since potential antagonism exists between Herba Andrographidis and endogenous progesterone, Herba Andrographidis should not be used during pregnancy (*2*, *61*).

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or paediatric use. Therefore, Herba Andrographidis should not be administered to children without medical supervision.

Adverse reactions

Large oral doses of Herba Andrographidis may cause gastric discomfort, vomiting and loss of appetite (*6*). These side-effects appear to be due to the bitter taste of andrographolide (*6*). Anaphylactic reactions may occur if the crude drug extract is injected (*6*, *56*). Two cases of urticaria have been reported (*18*).

Dosage forms

Crude drug, capsules, tablets and pills (*1*, *2*, *6*). Store in a well-closed container, protected from light and moisture.

Posology

(Unless otherwise indicated)

For pyrexia: a decoction from 3 g crude drug, twice daily (*1*, *5*). For the common cold: 1.5–3.0 g powdered crude drug three times daily, after meals and at bedtime (*1*). For diarrhoea: a decoction from 3–9 g crude drug as a single dose as needed (*1*, *5*), or two tablets of 500 mg four times daily, after meals and at bedtime (*5*).

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Radix Angelicae Sinensis

Definition

Radix Angelicae Sinensis consists of the dried roots of *Angelica sinensis* (Oliv.) Diels (Apiaceae) (*1*).

Synonyms

Although *Angelica sinensis* has also been referred to as *Angelica polymorpha* Maxim. var. *sinensis* (the latter being a synonym for *A. polymorpha* Maxim. (*2*)), their synonymy has not yet been firmly established (J.C. Regalado, personal communication, 1999). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Can qui, Chinese Angelica, dangdanggui, dang gui, dong quai, duong qui handanggui, hashyshat almalak, kara toki, langdu danggui, min-gui, tang-kuei, tangkuei tần qúi (*1*, *3–6*).

Geographical distribution

Indigenous to China (*3*, *4*).

Description

A fragrant, perennial herb, 0.5–1.0 m high. Stem glabrous and purplish, with light, linear striations. Inferior leaves tripinnate; superior leaves often pinnate; segments oval, dentate-incised, teeth obtuse. Petiole 3–11 cm long, sheathed; bracts rudimentary, not prominent. Umbels 10–14, radiate on top of the plant, rays irregular, interior margin uneven; bracteoles, narrow-linear 2–4; pedicels slender; carpophore bipartite; each umbel multiflorous (12–36 flowers); umbel stem 0.3–1.5 cm long. Flowers white, 5 petals, glabrous, incurvate at the tips. Carpels dorsally compressed, square-elliptical, the base cordiform, the tip rounded or lightly notched; dorsal veins 5, closely placed, projecting; central vein barely winged, marginal veins with very large wings; ducts oleaginous, 1 in each sinus, 2 in the commissure (*4*).

Plant material of interest: dried roots

General appearance

Somewhat cylindrical, 3–5 or more branches at the lower part, 15–25 cm long. Externally yellowish-brown to brown, longitudinally wrinkled and transversely lenticellate. Root stocks 1.5–4 cm in diameter, annulated, apex obtuse, showing purple or yellowish-green remains of stems and leaf sheaths; main roots lumpy on the surface, branching roots 0.3–1.0 cm in diameter, upper portion thick and lower portion thin, mostly twisted, with a few rootlet scars. Texture flexible, fracture yellowish-white or yellowish-brown, thick epidermis, showing some clefts and numerous brown spotted secretory cavities; wood paler in colour than the bark, cambium ring yellowish-brown (*1*).

Organoleptic properties

Odour: strongly aromatic; taste: sweet, pungent, slightly bitter (*1*).

Microscopic characteristics

Cork cells in several layers. Cortex narrow, with a few scattered oil cavities. Phloem cleft, broad (25–160 μm in diameter), relatively large on outer side, gradually becoming smaller, surrounded by 6–9 secretory cells, oil cavities and oil tubes. Cambium in a ring. Xylem rays, 3–5 cells wide; vessels scattered singly or in groups of 2–3, arranged radially; parenchymatous cells contain starch grains (*1*).

Powdered plant material

Yellowish-brown; parenchymatous cells in phloem are fusiform, with slightly thickened walls, very oblique criss-cross striations, thin transverse septa sometimes visible; scalariform and reticulate vessels frequent, up to 80 μm in diameter; fragments of oil cavities sometimes visible (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

Foreign organic matter

Free of foreign matter (*1*).

Total ash

Not more than 7.0% (*1*).

Acid-insoluble ash

Not more than 2.0% (*1*).

Alcohol-soluble extractive

Not less than 45% using 70% ethanol (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*8*). For other pesticides, see the *European pharmacopoeia* (*8*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*9*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*7*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, water-soluble extractive and loss on drying tests to be established in accordance with national requirements.

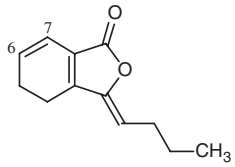
Chemical assays

Methods for both qualitative and quantitative determination of the alkyl phthalide components by high-performance liquid chromatography have been developed (*10*, *11*). National requirements for quantitative criteria should be established with respect to the concentration ranges reported for the essential oil (0.4–0.7%) (*4*) and ligustilide (0.5–5.0%) (*10*).

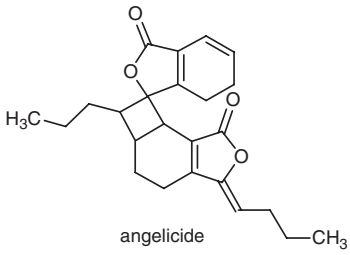
Major chemical constituents

The characteristic components are the simple alkyl phthalides (ligustilide, (*Z*)-ligustilide, (*Z*)-6,7-epoxyligustilide, angelicide, (*Z*)-butylidenephthalide, butylphthalide, 2,4-dihydrophthalic anhydride), which are the major components of the essential oil fraction of the roots. Other characteristic components of the oil have been identified as terpenes (β-cadinene, carvacrol and *cis*-β-ocimene). The non-volatile constituents reported are phenylpropanoids ((*E*)-ferulic acid,

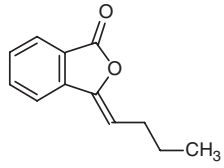
coniferyl ferulate); benzenoids (valerophenone-*o*-carboxylic acid and vanillic acid); and coumarins (angelol G, angelicone and umbelliferone) (*3*, *4*, *10*, *11*). It has been shown by high-performance liquid chromatography that the major chemical constituent of the roots is ligustilide, which can account for over 5% (*10*). Polysaccharide fractions of low relative molecular mass have also been reported (*12*, *13*). The structures of the characteristic constituents are presented below.



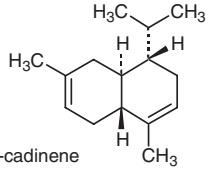
(*Z*)-ligustilide



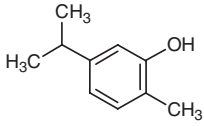
angelicide



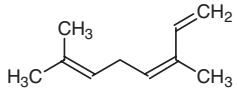
(*Z*)-butylidenephthalide
((*Z*)-ligusticum lactone)



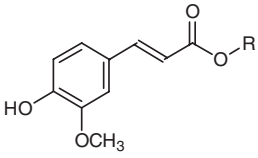
β-cadinene



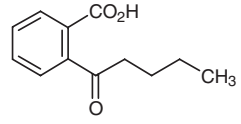
carvacrol



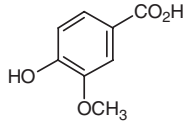
cis-β-ocimene



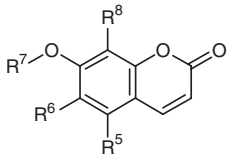
(*E*)-ferulic acid R = H
coniferyl ferulate R = Con



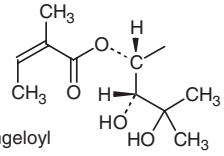
valerophenone-*o*-carboxylic acid
(ligusticumic acid)



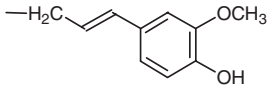
vanillic acid



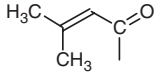
	R^5	R^6	R^7	R^8
umbelliferone	H	H	H	H
angelicone	OCH_3	H	CH_3	Sen
angelol G	H	Ang	CH_3	H



Ang = angeloyl



Con = (*E*)-coniferyl



Sen = senecioyl

Medicinal uses

Uses supported by clinical data

None. Although Radix Angelicae Sinensis has been alleged to be useful for the treatment of menopausal symptoms, a randomized, placebo-controlled clinical trial concluded that 4.5 g of the root daily for 24 weeks did not alleviate menopausal symptoms, such as hot flushes (*14*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of menstrual disorders such as irregular menstruation, amenorrhoea and dysmenorrhoea (*1*, *3*, *15–19*). As an analgesic for symptomatic treatment of rheumatic arthralgia, abdominal pain and in the management of post-operative pain (*1*, *20*). Treatment of constipation (*1*), anaemia (*1*, *20*), chronic hepatitis and cirrhosis of the liver (*20*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of dehydration, lumbago, abnormal menstruation, menopausal symptoms (including hot flushes), hypertonia and nervous disorders (*18*, *21*).

Pharmacology

Experimental pharmacology

Smooth muscle contraction

Hot aqueous extracts of Radix Angelicae Sinensis stimulated smooth muscle contractions of the bladder, intestine and uterus when administered intravenously to dogs (10 g/kg body weight) (*22*). Intravenous administration of an aqueous or 95% ethanol extract of the roots to cats, rats and rabbits increased the strength of the contractions and tone of uterine smooth muscles (*4*). In vitro assays demonstrated that a decoction of the roots stimulated the H_1 receptor of mouse uterus (*23*). The active constituent responsible for this activity is an aqueous- and alcohol-soluble, non-volatile component, the structure of which is unknown (*4*). Conversely, ligustilide, a constituent of the essential oil of the roots, inhibited contractions of isolated uteri from various animal models (*20*, *24*). Intraperitoneal administration of ligustilide (0.14 ml/kg body weight) to guinea-pigs inhibited asthmatic reactions induced by acetylcholine and histamine (*25*). Ligustilide (32.5–130.0 µl/ml) inhibited smooth muscle contractions induced by barium sulfate, acetylcholine and histamine in isolated guinea-pig trachea (*25*).

Antihepatotoxic activity

Intraperitoneal administration of a decoction of the roots (11 ml/kg body weight) ameliorated galactosamine-induced hepatotoxicity in rats (*26*). Ferulic

acid, a constituent of the roots, protected rat liver mitochondria against damage induced by oxygen free radicals (*27*). Intragastric pretreatment of mice with sodium ferulate (100 mg/kg body weight) daily for 10 days alleviated liver toxicity induced by paracetamol (*28*) and prednisolone (*29*), and bromobenzene-induced liver injury (*30*).

Cardiovascular activity

Cardiac haemodynamic studies demonstrated that intravenous administration of an aqueous root extract (2 g/kg body weight) to anaesthetized dogs increased coronary blood flow from 88 ml before administration to 128 ml (per 100 g cardiac muscle/minute post-injection). Coronary vascular resistance and myocardial oxygen consumption also decreased, while the heart rate decreased or remained unchanged (*31*). An extract of the roots increased coronary blood flow in isolated guinea-pig hearts (*32*).

In animal models, both aqueous and ethanol extracts of the roots had an effect on arrhythmias induced by epinephrine, barium chloride and digitalis (*32, 33*). Intravenous administration of an ethanol extract of the roots (4 g/kg body weight) antagonized chloroform- and epinephrine-induced arrhythmias in cats (*34*). Ethanol extracts of the roots and ferulic acid restored normal sinus rhythm after ouabain-induced arrhythmia in isolated ventricular muscle from cats (*20*). Aqueous extracts of the roots reduced the action potential amplitude and maximal upstroke velocity of the Q phase, and prolonged the effective refractory period and the duration of the action potential in guinea-pig myocardium (*35*). Intravenous administration of an aqueous extract of the roots (50 mg/kg body weight) to rabbits with ligation of the left anterior descending coronary artery provided protection against ischaemia- and reperfusion-induced myocardial dysfunction and injury (*36*). An aqueous extract of the roots bound to nitrendipine and diltiazem receptors, thereby demonstrating calcium channel blocking activity (*37*). A ligustilide dimer, isolated from the roots, inhibited [^{3}H]nitrendipine binding to dihydropyridine-sensitive calcium channels (inhibitory concentration of 50% [IC_{50}] 0.4 µmol/l) (*38*). Since calcium channel blockers are known to have pronounced effects on the cardiovascular system, this activity may explain some of the reported effects of root extracts on the cardiovascular system.

Antithrombotic activity

In vitro and in vivo studies have shown that extracts of the roots inhibit platelet aggregation and have antithrombotic activity (*20*). Aqueous extracts of the roots (200 mg/ml) or ferulic acid (0.4 mg/ml) inhibited platelet aggregation induced by ADP or collagen in vitro (*39*). A hot aqueous extract of the roots (500 mg/ml) or ferulic acid (1 mg/ml) inhibited thrombin-induced platelet aggregation and release of [^{3}H]5-hydroxytryptamine from labelled platelets in vitro (*39*). An aqueous extract of the roots inhibited both ADP- and collagen-induced platelet aggregation when administered intravenously to rats (200 mg/ml) (*20, 39*). The mechanism of action appears to be via inhibition of cyclooxygenase and throm-

boxane A_2 synthase by ferulic acid, leading to decreased production of thromboxane A_2 (*40*). The antithrombotic activity of the drug is associated with inhibition of platelet aggregation, reduction in the concentration of plasma fibrinogen, changes in cell surface charge and a decrease in blood viscosity (*20*).

Intraperitoneal administration of polysaccharides isolated from the roots increased haematopoiesis in mouse bone marrow, as determined by an increase in colony-forming units in the marrow cells (*12*, *41*). The polysaccharides promoted the proliferation and differentiation of haematopoietic progenitor cells in healthy and anaemic mice (*13*). Results of this study indicated that the polysaccharides may enhance haematopoiesis by stimulating macrophages, fibroblasts and lymphocytes in haematopoietic and muscle tissue to secrete haematopoietic growth factor (*13*).

Clinical pharmacology

Menstrual disorders

Although there are a number of case reports concerning the clinical use of Radix Angelicae Sinensis in the treatment of amenorrhoea and dysmenorrhoea, these studies were published between 1899 and 1910 (*15–18*). Randomized, controlled clinical trials are needed to confirm these observations. In these early case studies, female patients were treated with 5 ml of a fluidextract of the roots three times daily before meals for 1 week before menstruation. The treatment relieved premenstrual pain and induced menstrual flow in most cases. No abortifacient activity was observed in two pregnant women treated with the same fluidextract (*15*). In other studies, the fluidextract was used for the treatment of dysmenorrhoea in nulliparous women, and of severe bleeding in multiparous women. Administration of 5 ml of the fluidextract three times daily for 1 week before menstruation was effective in decreasing menstrual pain and chronic endometritis (*16*). Successful treatment of amenorrhoea and dysmenorrhoea in female patients was further reported after administration of the same fluidextract (5 ml, three times daily) (*17*, *18*). In another report, 112 women with dysmenorrhoea were treated for 3–7 days with ligustilide dimer isolated from the roots. The efficacy rate was 77%. Minor side-effects were nausea and dizziness, which disappeared after the treatment stopped (*42*).

Smooth muscle contraction

Decoctions of the roots reportedly stimulated uterine smooth muscle in female patients, but the doses used and the conditions being treated were not stated (*19*). A decoction of the roots lowered whole blood viscosity after administration to six patients (*11*).

Contraindications

Radix Angelicae Sinensis should not be administered to children or patients with diarrhoea, haemorrhagic diseases or hypermenorrhoea, and should not be used during pregnancy or lactation (*4*).

Warnings

No information available.

Precautions

Drug interactions

Decreased prothrombin times were reported in rabbits that received both a single subcutaneous dose of warfarin (2 mg/kg body weight) and a repeated oral dose of Radix Angelicae Sinensis (2 g/kg body weight twice daily for 3 days) (*43*). Therefore, patients receiving anticoagulant therapy should be advised against taking Radix Angelicae Sinensis without medical supervision.

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

Adverse reactions

Oral administration of Radix Angelicae Sinensis is generally regarded as having few side-effects; however, headaches may occur in sensitive individuals (*14*, *19*). No adverse reactions were reported in 40 people who received an aqueous root extract by intravenous administration (240 ml/person) for 30 days (*19*).

Dosage forms

Powdered crude drug and fluidextracts (*4*). Store in an airtight container in a cool, dry place protected from moisture (*1*).

Posology

(Unless otherwise indicated)
Daily dosage: 4.5–9 g crude drug (*1*).

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Flos Calendulae

Definition

Flos Calendulae consists of the dried ligulate florets or composite flowers of *Calendula officinalis* L. (Asteraceae) (*1–3*).

Synonyms

Asteraceae are also known as Compositae.

Selected vernacular names

Atunjaq, calendula, Chinese safflower, cuc kim tiên, djamir, djomaira, feminell, flamenquilla, fleur de calandule, fleur de souci, fleur de souci officinal, fleurs de tous les mois, garden marigold, gold-bloom, Goldblume, gole hamisheh bahar, hen and chickens, Körömvirag, lellousha, maravilla, marigold, mary-bud, ok-hhawan, pot marigold, qaraqus, qawqhan, quaqahan, ringflower, Ringelblüten, saialill, sciure'e Sant'antonio, souci, souci des jardins, tabsoult, toukinsenka, tousslat, uchu k'aspa, virreina, xu xi, zergul zerzira, zobeida, zubaydah (*4–7*).

Geographical distribution

Indigenous to central, eastern and southern Europe. Cultivated commercially in North America, the Balkans, Eastern Europe and Germany (*6*, *8*).

Description

An annual herb, much branched from the base, very aromatic, up to 0.3–0.6 m high; stem angular, hairy and solid. Leaves sessile, light green, with semi-amplexicaul base; entire, undulate or remotely denticulate; glandular hairs on both surfaces; lower leaves spatulate, obtuse, sometimes acute at the apex, 10–20 cm long and 1–4 cm wide; higher leaves oblong and mucronate, 4–7 cm long. Involucral bracts 7–15 mm long, covered with long, glandular hairs; inner involucral bracts with pellucid, scarious margin; marginal flowers in cultivated plants often multi-seriate; corolla oblong-spatulate, bright yellow or orange, 15–25 mm long and 3 mm wide, 1–3-toothed with 4 or 5 veins, marginally entire, covered at the base with patent, long, thick hairs; corolla of disc flowers rounded, 3-dentate top, 1.5–2.5 cm long and 4–7 mm in diameter, 5 mm long

tube and moderately widened limb. Stigma short, thick, hairy; ovary oblong, 0.5 mm in length, pubescent, shrivelling after anthesis. Achenes narrowly oblong, strongly curved, faintly ribbed, thinly pubescent or glabrous, 10–12 mm long, outer achenes warty-ribbed outside, inner achenes prickly-warty, often with broad, thick margins (*2*, *7*, *9*).

Plant material of interest: dried ligulate florets and composite flowers

General appearance

Ligulate florets consist of a yellow, orange or orange-yellow ligule, 3–5 mm wide and about 7 mm in the middle part, with 3-toothed apex and hairy, partly sickle-shaped, yellowish-brown to orange-brown tube with projecting style and 2-lobed stigma; occasionally with a partly bent yellowish-brown to orange-brown ovary. Tubular florets about 5 mm long, consist of yellow, orange-red or red-violet 5-lobed corolla and yellowish-brown or orange-brown tube, hairy in its lower part, mostly with a bent yellowish-brown to orange-brown ovary (*1*).

Organoleptic properties

Odour: faint, pleasantly aromatic (*10*, *11*); taste: bitter (*2*).

Microscopic characteristics

Inner epidermal cells of ray floret elongated, rectangular and almost straight-walled, cuticle faintly striated; stomata absent; outer epidermal cells similar, but with 3 or 4 anomocytic stomata; trichomes very numerous on the tube, bi-seriate; stigma epidermal cells straight-walled, polygonal. In disc floret, outer epidermal cells elongated, straight or slightly sinuous-walled, stomata absent; abundant trichomes on area below point of insertion of the stamens, mainly glandular, uniseriate or biseriate. Within the upper part of the anthers, a layer of isodiametric to elongated, moderately thick-walled, lignified and pitted cells; pollen grains spherical, up to 45 µm in diameter, with 3 germinal pores, exine finely granular with numerous short spines; apex of stigma covered by short, bulbous papillae (*2*).

Powdered plant material

Yellow-green; fragments of corollas containing light yellow oil droplets; some corollas with fairly large anomocytic stomata, others containing prismatic and very small clusters of calcium oxalate crystals. Covering trichomes biseriate, multicellular and conical; glandular trichomes with a uniseriate or biseriate, multicellular stalk and a large, ovoid, biseriate, multicellular head. Spherical

pollen grains up to 45 µm in diameter, exine finely granular with numerous short spines and with 3 germinal pores; occasional fragments of stigmas with short, bulbous papillae (*1*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for flavonoid content (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 5% bracts and not more than 2% other foreign matter (*1*, *2*).

Total ash

Not more than 10% (*1*, *2*).

Acid-insoluble ash

Not more than 2% (*2*).

Water-soluble extractive

Not less than 20% (*2*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

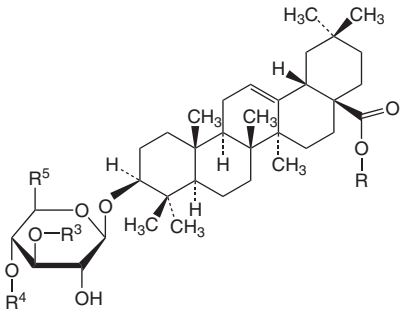
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

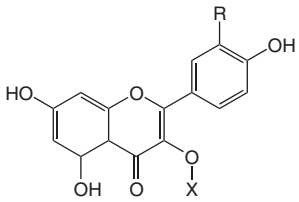
Chemical assays

Contains not less than 0.4% flavonoids, calculated as hyperoside, by spectrophotometry (*1*). A high-performance liquid chromatography method is also available (*15*).

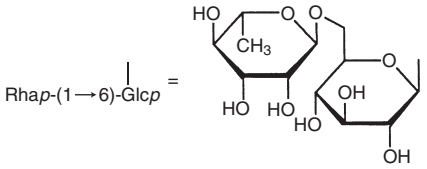
Major chemical constituents

The major constituents are triterpene saponins (2–10%) based on oleanolic acid (i.e. calendulosides) and flavonoids (3-*O*-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin. Other constituents include essential oil, sesquiterpenes (e.g. caryophyllene) and triterpenes (e.g. α- and β-amyrins, lupeol and lupenone) (*5*, *6*, *16*). Polysaccharides have also been reported (*17*). The structures of the characteristic triterpene saponins and flavonoids are presented below.





	R	X
astragalin	H	Glc*p*
hyperoside	OH	Gal*p*
isoquercitrin	OH	Glc*f*
rutin	OH	Rha*p*-(1→6)-Glc*p*



O-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

External treatment of superficial cuts, minor inflammations of the skin and oral mucosa, wounds and ulcus cruris (*2*, *18*, *19*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, angina, fevers, gastritis, hypotension, jaundice, rheumatism and vomiting (*2*, *5*, *6*).

Pharmacology

Experimental pharmacology

Phagocytosis

Three polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes in vitro in the colloidal carbon clearance test (*17*). Intraperitoneal injection of a polysaccharide fraction isolated from an aqueous extract of the flowers to mice (10 mg/kg body weight) enhanced phagocytosis (*20*). Intraperitoneal administration of an unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers weakly stimulated phagocytosis in mice inoculated with *Escherichia coli*. However, the hydroalcoholic extract was not active (*21*).

Antimicrobial activity

The essential oil of the flowers inhibited the growth in vitro of *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (*22*). A flavonoid fraction isolated from the flowers inhibited the growth in vitro of *S. aureus*, *Sarcina lutea*, *E. coli*, *Klebsiella pneumoniae* and *Candida monosa* (*23*). However, chloroform, ethanol, methanol or water extracts of the flowers did not inhibit bacterial growth in vitro (*24–26*). Acetone, ethanol or water extracts inhibited the growth in vitro of the fungus *Neurospora crassa* (*27*). Extracts of the flowers inhibited the growth in vitro of *Trichomonas vaginalis* (*28*). Oxygenated terpenes appear to be responsible for the antimicrobial activity (*29*).

Antiviral activity

A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses in vitro (*30*). However, an aqueous extract of the flowers was not active (*31*). A chloroform extract of the flowers inhibited the replication of HIV-1 in acutely infected lymphocytic MOLT-4 cells in vitro (IC_{50} 0.4 mg/ml) (*32*). A chloroform extract also inhibited HIV-1 reverse transcriptase activity in a dose-dependent manner (ED_{50} 51.0 µg/ml) (*32*). A 5% hot aqueous extract of the flowers (2 ml) inhibited the replication of encephalitis virus after intraperitoneal administration to mice (*33*).

Anti-inflammatory activity

Topical application of a 70% ethanol extract of the flowers to mice at a dose of 1.2 mg/ear (corresponding to 4.16 mg crude drug) reduced croton oil-induced ear oedema by 20% (*34*). External application of a carbon dioxide extract of the flowers (300 µg/cm^2) suppressed croton oil-induced ear oedema in mice (*34*). The triterpene fraction of an extract of the flowers had marked anti-inflammatory activity in mice (1 µg/ear) against ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*35*). Faradiol esters isolated from the flowers (240 µg/cm^2) inhibited croton oil-induced ear oedema in mice (*36*). Intragastric administration of an aqueous extract of the flowers (100 mg/kg body weight) inhibited carrageenan-induced footpad oedema in rats (*37*). However, an 80% ethanol extract of the flowers was weakly active (11% inhibition) at a concentration of 100 mg/kg body weight administered orally 1 hour prior to induction of oedema (*38*). Isorhamnetin glycosides isolated from the flowers inhibited rat lung lipoxygenase in vitro (*39*).

Wound-healing activity

External application of a hydroalcoholic extract accelerated the rate of contraction and epithelialization of excision wounds in rats (*40*). A 3% freeze-dried aqueous extract of the flowers induced vascularization in the chick chorioallantoic membrane assay. Histological sections of the treated chorioallantoic

membranes also indicated the presence of hyaluronan, a tissue glycosaminoglycan associated with neovascularization (*41*).

Clinical pharmacology

Although no randomized, controlled clinical trials have been performed, two case reports in the early medical literature support the traditional use of Flos Calendulae. The reports describe the use of a strong tincture of the flowers applied on compresses to reduce inflammation and suppuration, and to accelerate the healing of wounds (*42*, *43*). These reports may be of historical value only.

Contraindications

Flos Calendulae is contraindicated in cases of known allergy to plants of the Asteraceae (Compositae) family (*18*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Saponins isolated from Flos Calendulae were not mutagenic at a concentration of 400 µg/ml in the *Salmonella*/microsome assay using *S. typhimurium* strain TA98, with or without S9 metabolic activation (*44*). Extracts of the flowers were not carcinogenic after daily intragastric administration of 0.15 g/kg body weight to rats (for 22 months) or hamsters (for 18 months) (*45*). Mutagenicity testing of the fluidextract in the *Salmonella*/microsome assay (using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537) was negative at concentrations of up to 5 mg/plate. The mouse bone marrow micronucleus test was also negative after daily administration of up to 1 g/kg body weight for 2 days (*46*). A fluidextract of the flowers (100 mg/ml, 60% ethanol) was genotoxic in both mitotic crossing-over and chromosome segregation when assayed for mitotic segregation in the heterozygous diploid D-30 of *Aspergillus nidulans* (*46*).

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Calendulae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Weak skin-sensitization has been reported (*47*).

Dosage forms

Infusion for topical use; aqueous and alcohol extracts, tinctures and ointment for external use (*2*, *18*, *19*). Store in a well-closed container, protected from light (*1*).

Posology

(Unless otherwise indicated)
Topical application: an infusion of 1–2 g/150 ml (*18*). External use: a 40% alcohol extract (1 : 1), or tincture (1 : 5) in 90% alcohol (*2*). For the treatment of wounds, the tincture is applied undiluted; for compresses, the tincture is usually diluted at least 1 : 3 with sterile water (*18*, *48*, *49*). Ointment: 2–5% (*48*, *50*).

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Flos Caryophylli

Definition

Flos Caryophylli consists of the dried flower buds of *Syzygium aromaticum* (L.) Merrill et L.M. Perry (Myrtaceae) (*1–5*).

Synonyms

Caryophyllus aromaticus L., *Eugenia aromatica* (L.) Baill., *E. caryophylla* Thunb., *E. caryophyllus* (C. Spreng.) Bull. et Harr., *Jambosa caryophyllus* (Spreng.) Nied., *Myrtus caryophyllus* Spreng. (*1, 5–8*).

Selected vernacular names

Benefundi, choji, choko, chouji, choukou, clavero, clavo de olor, clous de girofle, clove, cloves, colve, ding huong, dingxiang, flores caryophylli, Gewürznelken, girofle, giroflier, glove, gurunful, harilik negipuu, kaan phluu, kaan pluu, kade, kanumfari, karafwu, karanho, kau-phlu, konofuru, koronfol, lauang, laung, lawang, Nägelein, osaragbogo-eze, qaranfal, qoranful, qronfel, szegfüszeg, ud-nuwwar (*1, 6–9*).

Geographical distribution

Indigenous to the Moluccas and southern Philippines, but currently cultivated in many tropical areas including Africa (e.g. Madagascar and United Republic of Tanzania), South America, Indonesia, Malaysia and Sri Lanka (*7,8*).

Description

Small evergreen trees, 10–20 m high. Leaves opposite, petiolate, lanceolate, pinkish to dark green, with translucent, aromatic glands, have a pungent odour when young. Inflorescence occurs as racemose panicles and bears buds that take on the form of nails before blossoming. Flowers red with 4 concave, overlapping petals that drop off as soon as the flower opens; stamens numerous; 4 calyx lobes. Fruit dark red, fleshy drupe. Buds readily exude oil when pressed or scratched with a fingernail (*7*).

Plant material of interest: dried flower buds

General appearance

Flower bud 10–20 mm long, bright reddish-brown to dark brown; lower part (the hypanthium) solid, cylindrical, somewhat flattened, 4-sided, tapering towards the base and bearing at the apex 4 thick, triangular, divergent sepals, alternating with 4 rounded, fragile, unexpanded, membranous, imbricated petals forming a pale, nearly spherical head that encloses numerous stamens, curved inward and inserted on a small disc, and a stiff, slender, erect, single style arising from a depression in the centre. Externally wrinkled; internally, hypanthium contains in its upper portion a 2-celled inferior ovary with numerous ovules attached to the axile placenta; has very large outer zone with numerous shining, oval oil glands near the periphery, numerous vascular bundles in the centre and a dark, lacunose layer abutting on the central zone and columella (*1*).

Organoleptic properties

Odour: characteristic, strongly aromatic; taste: pungent, spicy, followed by slight numbness (*1*, *3*, *5*).

Microscopic characteristics

Hypanthium epidermis of small, thick-walled isodiametric cells with very thick cuticle, with stomata with no special subsidiary cells. Parenchymatous layer containing numerous large (up to about 200 µm long), oval, radially elongated, schizo-lysigenous oil glands, arranged in 2 or 3 more or less intermixed layers. Layer of parenchyma and collenchyma containing clusters of calcium oxalate crystals, and traversed by small, irregularly arranged vascular bundles consisting of delicate, spiral vessels (up to 20 µm in diameter), usually accompanied by isolated fusiform, pericyclic fibres (200–650 µm long and up to 40 µm in diameter), having strongly thickened lignified walls. Lacunous layer formed of thin-walled parenchyma. The columella consists of a parenchymatous strand with numerous closely arranged, small vascular bundles. Sepals, with epidermis resembling that of hypanthium and having numerous stomata on outer surface; mesophyll with rounded or stellate cells, numerous ovoid oil glands and clusters of calcium oxalate crystals, and traversed by a few slender vascular bundles. Petals, with epidermis formed of cells with straight, thin walls; stomata, absent; mesophyll, undifferentiated, containing oil glands and cells with clusters of calcium oxalate crystals, and traversed by small vascular bundles. Stamens, with filaments having a central vascular strand and oil glands beneath the epidermis; connective tissue, with a large oil gland in the apex of anther walls, with fibrous layer and minute clusters of calcium oxalate crystals along the line of dehiscence. Pollen grains, triangular, tricolpate, 10–20 µm in diameter. Style, with epidermis similar to that of hypanthium, and consisting of small collenchyma cells, with clusters of calcium oxalate crystals, radially elongated oil glands, and traversed by 2 narrow vascular strands (*1*).

Powdered plant material

Dark brown; abundant fragments of collenchyma and parenchyma with clusters of calcium oxalate crystals, fragments of epidermis with thick-walled cells and few stomata; fragments of vascular or parenchyma tissue showing broken or entire oil glands; numerous fragments of vascular bundles with delicate spiral vessels, ranging from 6 to 45 µm in diameter, mostly 6–10 µm; occasional fusiform, rather thick-walled fibres, 4–20 µm wide; numerous pollen grains, appearing either as equilateral triangular, with truncated, emarginate apices, or oval in outline, 10–20 µm in diameter; fragments of the fibrous layer of anther wall; clusters of calcium oxalate crystals, 10–15 µm in diameter (*1*, *5*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of eugenol and β-caryophyllene (*1*, *3–5*, *10*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Foreign organic matter

Not more than 4% open buds, peduncles and fruits; not more than 2% deteriorated buds; not more than 0.5% other foreign matter (*5*).

Total ash

Not more than 7% (*4*, *5*).

Acid-insoluble ash

Not more than 0.5% (*4*).

Sulfated ash

Not more than 8% (*12*).

Loss on drying

Not more than 12% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the

WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Other purity tests

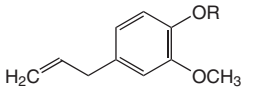
Chemical, water-soluble extractive and alcohol extractive tests to be established in accordance with national requirements.

Chemical assays

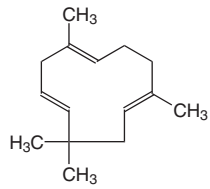
Contains not less than 15% (v/w) essential oil (*1*, *12*), determined by distillation (*5*).

Major chemical constituents

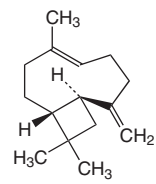
The major constituent (up to 20%) is an essential oil, which is characterized by the presence of eugenol (60–95%), eugenol acetate (2–27%), and α- and β-caryophyllene (5–10%) (*6*, *8*, *9*, *14*, *15*). The structures of the major constituents are presented below.



eugenol R = H
eugenol acetate R = CO-CH_3



α-caryophyllene



β-caryophyllene

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

External or local applications for the treatment of toothache, and minor infections of the mouth and skin (*7*, *14*, *16*). Also used as an antiseptic for dressing

of minor wounds, and, in the form of lozenges, for sore throats and coughs associated with the common cold (*7*). The essential oil (1–5%) is used in mouthwashes (*16*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, bleeding gums, dyspepsia, fevers and morning sickness (*9*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Ethanol (95%) or aqueous extracts of Flos Caryophylli inhibited the growth in vitro of *Staphylococcus aureus* (*17*). The juice of the flower bud inhibited the growth in vitro of *Mycobacterium tuberculosis* (minimal inhibitory concentration [MIC] 1:160) (*18*). The powdered crude drug inhibited the growth in vitro of *Yersinia enterolitica* when added to the medium at a concentration of 1–3% (w/w) (*19, 20*). An aqueous extract of the flower buds inhibited the growth in vitro of *Bacillus subtilis* (*21*). A chloroform extract of the flower buds inhibited the growth in vitro of *Cladosporium werneckii* (*22*). A 50% ethanol extract of the flower buds inhibited the growth of *Aspergillus fumigatus, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum, Penicillium digitatum, Rhizopus nigricans, Trichophyton mentagrophytes, Candida albicans* and *Saccharomyces pastorianus* at a concentration of 500 mg/ml (*23*).

Eugenol, one of the active constituents of the flower buds, inhibited the growth in vitro of *Staphylococcus aureus, Propionibacterium acnes* and *Pseudomonas aeruginosa*, with an MIC of 0.05, 0.05 and 0.80 mg/ml, respectively (*24, 25*). In other studies, eugenol had a broad spectrum of antibacterial activity in vitro, inhibiting the growth of *Clostridium sporogenes, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella pullorum, Staphylococcus aureus, Streptococcus faecalis* and *Comamonas terrigena* at various concentrations (*26, 27*). Eugenol also had a broad spectrum of antifungal activity in vitro, inhibiting the growth of *Alternaria alternata, Aspergillus fumigatus, Aspergillus niger, Aspergillus flavus, Cladosporium werneckii, Cladosporium cucumerinum, Colletotrichum capsici, Helminthosporium oryzae, Microsporum canis, Penicillium expansum, Phytophthora parasitica, Rhizopus nodosus, Trichophyton mentagrophytes* and *T. rubum* at various concentrations (*27–30*).

Antiviral activity

An aqueous extract of the flower buds suppressed the replication of herpes simplex virus (HSV) in vitro at a concentration of 50 µg/ml (*31*). An aqueous extract of the flower buds had antiviral activity against HSV-1 in vitro (IC_{50} 60 µg/ml), and in mice (250 mg/kg body weight by gastric lavage) (*32*). A hot

aqueous extract of the flower buds suppressed the replication of HSV-1, measles virus and poliovirus-1 in Vero cells in vitro at a concentration of 0.5 mg/ml (*33*). Intragastric administration of a decoction of the flower buds (750 mg/kg body weight) decreased HSV-1 genome titres and the severity of HSV infection in mice with recurring herpetic lesions induced by ultraviolet light (*34*). Eugenol at a concentration of 0.1–10 µg/ml demonstrated antiviral activity against HSV and adenovirus-6 in vitro (*35*). Eugeniin isolated from the flower buds exhibited anti-HSV-1 activity in mice (*36*).

Anti-inflammatory activity

Topical application of a methanol extract of the flower buds (2 mg/ear) suppressed ear oedema in mice induced by 12-*O*-tetradecanoylphorbol-13-acetate (*37*). A methanol extract of the flower buds inhibited interleukin-8 production induced by lipopolysaccharide in rat macrophages in vitro at a concentration of 0.1 mg/ml (*38*). Administration of eugenol (100 mg/kg body weight by gastric lavage or 50 mg/kg body weight intraperitoneally) inhibited carageenan-induced footpad oedema in rats (*39–41*). Intragastric administration of eugenol to rats (33 mg/kg body weight) suppressed footpad and knee oedema induced by *Mycobacterium tuberculosis* (*42*). Administration of eugenol to rats (50 mg/kg body weight intraperitoneally or 100 mg/kg body weight by gastric lavage) inhibited carrageenan-induced footpad oedema (*39, 41*). Topical application of eugenol to mice and rats at a dose of 0.2–2.0 mg/ear suppressed ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate and ethyl phenylpropiolate (*43–45*). Topical application of eugenol inhibited carrageenan-induced footpad oedema in rats and reversed passive Arthus reaction in rabbits (*46*). Eugenol inhibited the activities of cyclooxygenase (IC_{50} 12–82 µmol/l) and lipoxygenase (IC_{50} 20–100 µmol/l) in vitro (*41, 46–48*). Eugenol also inhibited the biosynthesis of prostaglandin and thromboxane in various biological systems (*27, 44, 49–51*) and both eugenol and isoeugenol inhibited platelet aggregation (IC_{50} 1.8 µmol/l) (*46*).

Antioxidant activity

A petroleum ether or ethylene chloride extract of the flower buds exhibited strong antioxidant activity in vitro at a concentration of 0.1% (*52, 53*). A methanol extract of the flower buds inhibited lipid peroxidation induced by carbon tetrachloride, ADP plus arachidonic acid, and ADP plus NADPH (IC_{50} 1.7, 2.6 and 6.4 µg/ml, respectively) (*54*). The antioxidant activity of eugenol has been demonstrated in a wide range of in vitro systems (*55–59*).

Miscellaneous activities

The essential oil had spasmolytic activity in vitro on isolated guinea-pig trachea and intestine (*60, 61*). Eugenol and caryophyllene had a narcotic effect after intravenous administration of high doses (200–400 mg/kg body weight) (*27, 62*), and a sedative effect after intragastric administration of low doses (1–100 mg/kg body weight) to mice (*60*).

Clinical pharmacology

None.

Contraindications

Flos Caryophylli is contraindicated in cases of known allergy to plants of the Myrtaceae family.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous or chloroform–methanol extract of the crude drug was not mutagenic in the *Salmonella*/microsome assay at concentrations up to 100 mg/ml (*63*, *64*). A hot aqueous extract was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 or TA100 at a concentration of 50 mg/disk (*63*, *65*). However, a 95% ethanol extract was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA102 at a concentration of 10 mg/plate (*66*). Eugenol was not mutagenic in vitro (*Salmonella*/microsome assay; up to 600 µg/plate) or in vivo (in mice; 200 mg/kg body weight, by intramuscular injection) (*67–69*). Local application of eugenol reduced the carcinogenic activity of benzopyrene (*70*).

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Caryophylli should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Allergic contact dermatitis has been reported in patients who were regularly exposed to Flos Caryophylli or who already had dermatitis of the fingertips (*71*).

Dosage forms

Crude drug, extracts, tincture (1:5, 25% ethanol), lozenges and mouthwash. Store in a well-closed container, protected from light (*1*, *5*).

Posology

(Unless otherwise indicated)

Daily dosage: crude drug 3–5 g as an infusion (preferably taken hot), three times daily; 25% ethanol extract (1:1) 3–5 ml; tincture (1:5, 25% ethanol) 10–25 ml (2).

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Rhizoma Cimicifugae Racemosae

Definition

Rhizoma Cimicifugae Racemosae consists of the dried rhizomes and roots of *Cimicifuga racemosa* (L.) Nutt. (Ranunculaceae) (*1*)[1].

Synonyms

Actaea gyrostachya Wender, *A. orthostachya* Wender, *A. monogyna* Walt., *A. racemosa* L., *Bortrophis actaeoides* Raf., *B. serpentaria* Raf., *Christophoriana canadensis racemosa* Gouan, *Cimicifuga racemosa* (Torr) Bart., *C. serpentaria* Pursh, *Macrotis racemosa* Sweet, *M. serpentaria* Raf., *Macrotrys actaeiodes* Raf. (*4–6*).

Selected vernacular names

Actée à grappes, black cohosh, black root, black snakeroot, bugbane, bugwort, bugwort rattleroot, cimicifuga, cohosh bugbane, Frauen Wurzel, herbe aux punaises, macrotnys, macrotys, macroty's, natsushirogiku, Qatil el baq, racine d'actée à grappes, rattle root, rattle snake root, rattle top, rattleweed, rich weed, schwarze Schlangenwurzel, squaw root, squawroot, Traubensilberkerze, Wanzenkraut, zilberkaars (*7–9*).

Geographical distribution

Indigenous to eastern North America (*9*).

Description

A perennial herb, up to 1–2.5 m high; subterranean part consists of a thick, knotted rhizome system. Leaves compound, pinnate, up to 7 cm long; leaflets serrate along the margin, subcordate to subcuneate at the base. Inflorescence a long, wand-like raceme of white flowers with numerous stamens (*9*, *10*).

[1] Rhizomes and roots of *Cimicifuga heracleifolia* Kom., *C. dahurica* (Turcz.) Maxim. or *C. foetida* L. are referred to as Rhizoma Cimicifugae in the *Pharmacopoeia of the People's Republic of China* (*2*). Rhizomes and roots of *C. simplex* Warm. and related species are referred to under the same name in *The Japanese pharmacopoeia* (*3*).

Plant material of interest: dried rhizomes and roots

General appearance

Mixture of entire and broken dried rhizomes and roots. Rhizome dark-brown, hard, sub-cylindrical and somewhat knotted; 1–2.5 cm in diameter and 2–15 cm long, with numerous, closely-arranged, upright or curved branches, each terminating in the remains of a bud or a circular, cup-shaped scar; branches about 1 cm in diameter and up to 3 cm long, marked with distinct, encircling leaf scars; fracture horny; transverse surface showing a thin outer bark surrounding a ring of numerous pale, narrow wedges of vascular tissue alternating with dark medullary rays; a large central pith.

Roots attached to under surface of the rhizome or, more usually, broken off leaving circular scars. Roots dark brown, 1–3 mm in diameter, brittle, nearly cylindrical or obtusely quadrangular, longitudinally wrinkled; fracture short; transverse surface showing a distinct cambium line separating the wide outer bark from the central region composed of 3–6 wedges of lignified xylem tissue united at their apices and separated by broad, non-lignified medullary rays (*1*, *9*).

Organoleptic properties

Odour: slight; taste: slightly bitter (*1*, *9*).

Microscopic characteristics

Rhizome: yellowish-brown, suberized epidermis, several layers of starch- and resin-containing cortical parenchyma, 2 circles of open, collateral, fibrovascular bundles, the outer bundles being smaller than the inner; medullary rays separate the bundles and contain starch grains, spherical or polygonal, simple or 2–3 or even up to 6 compound; individual grains 3–15 μm in diameter with central slit-shaped hilum. Xylem contains tracheae with bordered pits and numerous strongly lignified wood fibres; and a central pith with cells resembling those of the cortex.

Root: thin epidermis, a cortex, separated into 2 zones by a distinct endodermis, and 4–6, occasionally 3, open, collateral fibrovascular bundles separated by broad, wedge-shaped medullary rays (*1*, *9*).

Powdered plant material

Light brown, odourless with a bitter taste; abundant starch grains, often occurring in masses in numerous fragments of thin-walled parenchyma; groups of small, lignified vessels with closely arranged bordered pits or, less frequently, with reticulate thickening; lignified thin-walled fibres and xylem parenchyma; fragments of brown suberized cells with thickened walls (*1*).

General identity tests

Macroscopic and microscopic and microchemical examinations (*1*, *9*), and thin-layer chromatography for the presence of characteristic flavonoids and phenolic acids (*1*, *11*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 5% stem bases and not more than 2% other foreign matter (*1*).

Total ash

Not more than 10% (*1*).

Acid-insoluble ash

Not more than 4% (*1*).

Water-soluble extractive

Not less than 10% (*1*).

Loss on drying

Not more than 12% (*5*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

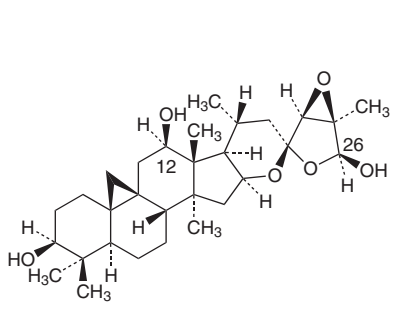
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

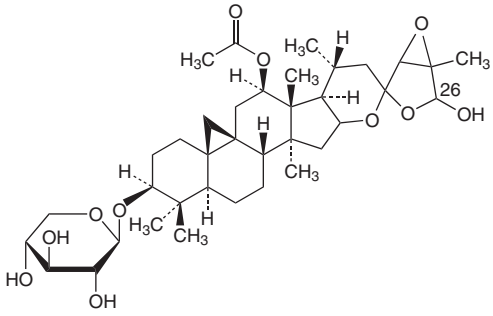
Qualitative assessments may be based on the triterpene and isoflavonoid content. Concentration ranges and quantitative methods need to be established. A high-performance liquid chromatography method is available for the quantitative analysis of flavones (*15*).

Major chemical constituents

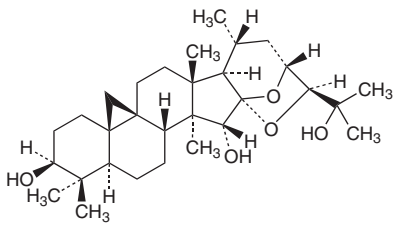
The major and characteristic constituents include the cycloartanol-based triterpenes acteol, acetylacteol, 26-deoxyacteol, cimigenol, actein, 26-deoxyactein and cimicifugoside. (*E*)-Isoferulic acid and the isoflavone formononetin are also found (*4*, *15–17*). However, the latter compound could not be detected in alcohol extracts of the root (*15*). The structures of the representative constituents are presented below.



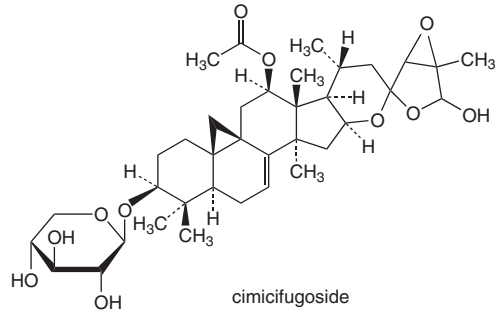
acteol



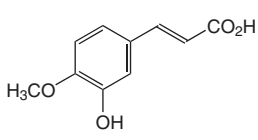
actein



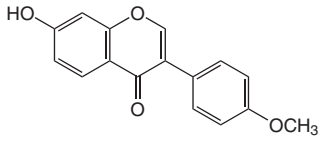
cimigenol



cimicifugoside



(*E*)-isoferulic acid



formononetin

Medicinal uses

Uses supported by clinical data

Treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability (*18–26*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of premenstrual syndrome and dysmenorrhoea (*27*, *28*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of coughs, dyspepsia, epilepsy, intercostal myalgia, rheumatoid arthritis, sciatica, snake bites, tinnitus and whooping cough (*1*, *8*, *9*, *28*, *29*).

Pharmacology

Experimental pharmacology

Estrogenic activity

The estrogenic effects of Rhizoma Cimicifugae Racemosae are controversial, and have been assessed both in vitro and in vivo. The in vitro proliferation of human mammary carcinoma cells (cell line 435) was measured after treatment with an isopropyl alcohol extract of the rhizome. Treatment using concentrations below 2.5 µg/ml did not enhance growth of the cells. However, concentrations of 2.5 µg/ml and above significantly inhibited cell proliferation (*30*). Similar results were obtained using the estrogen receptor-positive human mammary carcinoma cell line MCF-7. When these cells were treated with a 40% isopropyl alcohol extract of the rhizome at concentrations ranging from 1 ng/ml to 100 µg/ml, the extract induced a dose-dependent inhibition of cell proliferation and also augmented the antiproliferative effects of tamoxifen (*31*). An extract of the rhizome (extract not specified) was tested in vivo for possible estrogenic effects in female rats. The extract was added to a standard liquid diet and fed to ovariectomized rats daily for 3 weeks. An increase in uterine weight was observed, along with an increase in serum ceruloplasmin levels, suggesting estrogenic activity of the extract (*32*). However, in a short-term study, intragastric or subcutaneous administration of a 50% ethanol extract of the rhizome (30, 300 or 3000 mg/kg body weight) to immature mice daily for 3 days did not have any estrogenic effects, as assessed by changes in uterine weight and vaginal cytology (*33*). Constituents of a chloroform fraction, isolated from a methanol extract of the rhizome, bound to the estrogen receptors of isolated rat uteri in vitro. Formononetin, a minor constituent of the extract, showed a low binding affinity to the estrogen receptor (11.5 mmol/l) (*34*). The effects of formononetin and a dichloromethane extract of the rhizome on luteinizing hormone secretion were tested in vivo (*35*). Ovariectomized rats received nine intraperitoneal injections over 5 days (equivalent to a total

dose of 10 mg formononetin or 108 mg extract). The extract, but not formononetin, reduced the serum concentration of luteinizing hormone (*34*, *35*). Intraperitoneal (but not intragastric) administration of a chloroform (140 mg), 60% ethanol (0.3 ml) or dichloromethane (27 mg) extract of the rhizome reduced the serum concentration of luteinizing hormone in ovariectomized rats after 3–3.5 days of treatment (*34*, *36*, *37*). Serum follicle-stimulating hormone and prolactin levels, however, were not affected (*34*). Intragastric administration of a 95% ethanol extract of the rhizome (0.05 ml/animal daily) had no effect on genital functions in female mice (*38*).

The effects of estradiol on estrogen-dependent brain and uterine functions were compared with those of a dichloromethane fraction of a hydroalcoholic rhizome extract. Daily injection of the extract (60 mg/rat) or estradiol for 3 weeks reduced serum luteinizing hormone levels, but only estradiol increased uterine weight. Up-regulation of estrogen receptor-α gene expression was observed in MCF-7 mammary carcinoma cells treated with either the extract (35 µg/ml) or estradiol. The results suggest that the dichloromethane fraction of the extract may act as a selective modulator of the estrogen receptor (*39*).

Anti-inflammatory activity

Subcutaneous injection of an ethanol extract of the crude drug (100 mg/kg body weight) reduced carrageenan-induced footpad oedema in rats by 32% (*40*).

Clinical pharmacology

Climacteric symptoms

The following studies were all performed using oral administration of either a 40% isopropyl alcohol or 60% ethanol extract of Rhizoma Cimicifugae Racemosae.

In a placebo-controlled clinical trial, 110 women with climacteric symptoms were treated with the ethanol extract (8 mg daily) for 2 months. Although a significant reduction in serum luteinizing hormone levels was observed in the treated group ($P < 0.01$), there was no effect on follicle-stimulating hormone levels (*37*).

A 12-week double-blind, placebo-controlled study of 80 women (aged 45–58 years) compared the efficacy of the rhizome extract (8 mg daily) with either conjugated estrogens (0.625 mg daily) or placebo for the treatment of climacteric symptoms and vaginal atrophy. The group treated with the extract showed a greater reduction in climacteric symptoms than groups treated with either conjugated estrogens or placebo, as demonstrated by a significant reduction in both the Kupperman Index and Hamilton Rating Scale for Anxiety (Hamilton Anxiety Rating Scale), and by the proliferative status of the vaginal epithelium ($P < 0.001$) (*23*).

The efficacy of the isopropyl alcohol extract for the treatment of climacteric symptoms induced by hysterectomy was assessed in a randomized comparison trial without controls. Sixty women under the age of 40, who had

undergone a hysterectomy, but retained one ovary, were treated daily with either the extract (8 mg), estriol (1 mg), conjugated estrogens (1.25 mg) or an estrogen–progesterone combination. After 4, 8, 12 and 24 weeks of treatment, a significant decrease in climacteric symptoms was reported by the patients in all treatment groups ($P < 0.01$). This was verified by a reduction in a modified Kupperman index. Conjugated estrogens or the estrogen–progesterone combination appeared to be slightly more effective than the extract; however, no significant difference between the three treatments was observed. Serum levels of luteinizing hormone and follicle-stimulating hormone did not change significantly in any of the groups ($P > 0.05$) (*20*).

In a study without controls of 50 women with climacteric complaints, after administration of the ethanol extract (40 drops twice daily for 12 weeks), patients with moderate symptoms required no further treatment (*25*).

A randomized controlled trial involving 60 women aged 45–60 years compared the efficacy of the ethanol extract with hormone replacement therapy (0.6 mg conjugated estrogens) or 2 mg diazepam for the treatment of climacteric symptoms. Clinical assessment of the patients was based on three indicators: the menopause index (for hot flushes, nocturnal sweating, nervousness, headache and palpitations), and the Hamilton Anxiety Rating Scale and self-assessment depression scale (for psychological symptoms). Patients were treated with either the extract (40 drops twice daily), conjugated estrogens (0.625 mg daily) or diazepam (2 mg daily) for 12 weeks. All three forms of therapy reduced all three indicators. The extract and conjugated estrogens also reduced atrophic changes in the vaginal mucosa (*26*).

In a study without controls, 36 women with climacteric symptoms were treated with the ethanol extract (40 drops) twice daily for 12 weeks. A significant decrease in the average values of the Kupperman index was reported ($P < 0.001$), and an increase in the values of the Clinical Global Impression scale was observed (*18*).

A placebo-controlled clinical trial assessed the efficacy of a rhizome extract for the treatment of 82 women with climacteric symptoms. In the group treated with the extract, 31 women reported a considerable decrease in symptoms, while 10 women with severe climacteric symptoms did not show improvement. In the placebo group, a reduction of symptoms was seen in four women; symptoms were unchanged in 37 women (*19*).

In a study without controls, 50 women with climacteric symptoms, who had received at least one or two intramuscular injections of estradiol valerate (4 mg) and prasterone enantate (200 mg) during 1–2 months prior to the trial, were treated with the isopropyl alcohol extract (2 tablets twice daily) for 6 months. The therapeutic results were rated as good to very good in 41 of the patients: during the treatment period 28 required no further injections, 21 patients required one injection and one patient required two injections. The Kupperman index decreased significantly ($P < 0.001$), indicating successful treatment of symptoms (*22*).

A multicentre, drug-monitoring study without controls of 629 women with climacteric symptoms assessed the efficacy of the ethanol extract (40 drops

twice daily) for 8 weeks. Symptoms improved in over 80% of all patients after 6–8 weeks of treatment (*24*).

A 6-month randomized, double-blind clinical trial compared two different doses of the isopropyl alcohol extract (40 and 127 mg daily) in 152 women with climacteric symptoms. A decrease in the Kupperman index was observed after 2 weeks in both treatment groups. Both dosages showed similar levels of efficacy and safety. After 6 months, approximately 90% of patients had responded to the treatment. No effects on vaginal cytology or the levels of luteinizing hormone, follicle-stimulating hormone, sex hormone binding-globulin, prolactin and estradiol were observed (*21*, *41*, *42*).

A review of eight clinical trials assessed the efficacy of extracts of the crude drug for the alleviation of climacteric symptoms in women. It concluded that preparations of the rhizome may be a safe and effective alternative to estrogen replacement therapy for patients for whom the replacement therapy is contraindicated or refused (*43*).

General gynaecological disorders

Five case studies have described the successful use of a 40% isopropyl alcohol or 60% ethanol extract of the rhizome in the treatment of a total of 833 women with gynaecological disorders (e.g. climacteric symptoms) and menstrual disorders (e.g. primary or secondary amenorrhoea, and premenstrual disorders) (*44–48*).

Contraindications

Owing to its potential estrogenic effects (*39*) and the lack of data on its safety, Rhizoma Cimicifugae Racemosae should not be used during pregnancy or lactation, or in children under the age of 12 years.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A 40% isopropyl alcohol extract of the crude drug was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 or TA100 (*16*).

Pregnancy: teratogenic effects

Intragastric administration of up to 2 g/kg body weight of the crude drug, as a component of two traditional Chinese medicines, to pregnant rats daily on days 7–17 of gestation was not teratogenic (*49*, *50*). (See also Contraindications.)

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions or drug and laboratory test interactions.

Adverse reactions

Minor gastrointestinal upset and headache (*19*, *23–25*).

Dosage forms

Crude drug, and isopropyl alcohol or ethanol extracts (*16*). Store in a well-closed container, protected from light and moisture.

Posology

(Unless otherwise indicated)
Daily dosage: 40–60% isopropyl alcohol or ethanol extracts of the crude drug (*18–20*, *22–26*, *37*, *42*), corresponding to 40 mg drug (*27*).

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Folium cum Flore Crataegi

Definition

Folium cum Flore Crataegi consists of the dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm), *C. laevigata* (Poir.) DC, their hybrids or, more rarely, other *Crataegus* species (Rosaceae).[1]

Synonyms

Crataegus monogyna Jacq. (Lindm): *C. apiifolia* Medik. non Michx., *C. oxyacantha* L. ssp. *monogyna* Lev., *Mespilus elegans* Poir., *M. monogyna* All., *M. monogyna* Ehrh. (*3*).

Crataegus laevigata (Poir.) DC: *C. oxyacantha* L., *C. oxyacantha* L. ssp. *polygala* Lev., *C. oxyacanthoides* Thuill, *Mespilus oxyacantha* (Gartn.) Crantz. (*1*, *3*, *4*).

Selected vernacular names

Aubeline, aubepine, biancospino, calabrice, calavrice, eenarijlige meidorn, eenstijlige meidorn, eingriffeliger Weissdorn, Einkern-Weissdorn, épine blanche, espinero, espino blanco, espino majuelo, galagonya virágzó ágvég, hagdorn, hagedorn, harthorne, haw, hawthorn, hedge thorn, majuelo, may, May thorn, Mehlbeerbaum, Mehldorn, seiyosanzashi, shanzha, sorkh valik, spina, Stumpf gelappter Weissdorn, Weissdorn, whitethorn, za bur, zu'rurr el awdiyah, zweigriffeliger Weissdorn, Zweikern-Weissdorn (*1*, *3*, *5–8*).

Geographical distribution

Common to the temperate areas of the northern hemisphere, including eastern areas of North America, parts of South America, east Asia and Europe (*9*, *10*).

Description

Crataegus monogyna: a thorny shrub; leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*. Flowers, grouped into

[1] Fructus Crataegi is included in the *European pharmacopoeia* (*1*) and in the pharmacopoeia of the People's Republic of China (*2*). However, clinical and pharmacological data for this plant part are insufficient to justify monographing at this time.

branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, stamen with black anthers and 1 style (*1*, *9*).

Crataegus laevigata: a thorny shrub; twigs glabrescent, brown; leaves bright green, obovate, with 3, 5 or 7 shallow, obtuse lobes. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles; fruits deep red, globose or ellipsoid (*9*, *11*).

Plant material of interest: dried leaf with flower

General appearance

Crataegus monogyna: leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*, with secondary venation curved outwards. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, anthers black with 1 style; sepals lanceolate, acuminate, falling over the ovary after flowering (*1*, *9*).

Crataegus laevigata: leaves bright green with 3, 5 or 7 shallow, obtuse, converging lobes, with secondary venation curved inward. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles.

Organoleptic properties

Odour: characteristic, faint; taste: slightly bitter-sweet, astringent (*12–15*).

Microscopic characteristics

Leaf dorsoventral; cells of upper epidermis polygonal, straight-walled with striated cuticle, those of lower epidermis more sinuous; anomocytic stomata on lower epidermis only; covering trichomes on both epidermises but more numerous on the lower, which are long, tapering, unicellular or very occasionally uniseriate with 2 cells, walls moderately thickened; cluster crystals or groups of small prismatic crystals of calcium oxalate in the cells along the veins. Epidermis of floral pedicel and receptacle contain abundant covering trichomes similar to those on the leaf, but longer and more undulating; calyx with numerous anomocytic stomata on the outer epidermis, inner epidermis with a striated cuticle; epidermal cells of corolla distinctly papillose; fibrous layer of anther with characteristic thickenings; pollen grains spherical to elliptical, up to 45 µm in diameter, with 3 germinal pores and faintly granular exine. Epidermal cells

of stem have thickened anticlinal outer walls; cortex parenchymatous with prismatic and cluster crystals of calcium oxalate; dense groups of small, tightly packed pericyclic fibres with much thickened and lignified walls; xylem completely lignified, composed of scattered vessels, thick-walled fibres and parenchyma separated by distinct medullary rays containing brown-coloured matter; larger vessels with bordered pits, smaller elements with annular or spiral thickening; central pith parenchymatous and lignified, cells with moderately thickened walls and numerous pits (*12*, *15*).

Powdered plant material

Yellowish-green. Unicellular covering trichomes, usually with a thick wall and wide lumen, almost straight or slightly curved, pitted at the base; fragments of leaf epidermis with cells which have sinuous to polygonal anticlinal walls and large anomocytic stomata surrounded by 4–7 subsidiary cells; parenchymatous cells of mesophyll containing cluster crystals of calcium oxalate, usually 10–20 µm in diameter; cells associated with veins contain groups of small prismatic crystals. Petal fragments showing rounded polygonal epidermal cells, strongly papillose, thick walls with clearly visible wavy striations in the cuticle; anther fragments showing endothecium with an arched and regularly thickened margin. Stem fragments containing collenchymatous cells, bordered, pitted vessels and groups of lignified sclerenchymatous fibres with narrow lumina. Numerous spherical to elliptical or triangular pollen grains up to 45 µm in diameter, with 3 germinal pores and a faintly granular exine (*1*).

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography (*1*, *7*), and microchemical test for the presence of procyanidins (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Foreign organic matter

Not more than 8% lignified branches with a diameter greater than 2.5 mm (*1*) and not more than 2% other foreign matter (*1*, *15*).

Total ash

Not more than 10% (*1*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Other purity tests

Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues

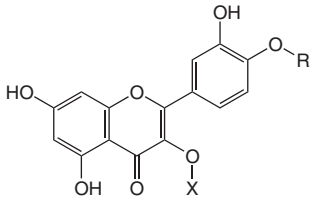
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Chemical assays

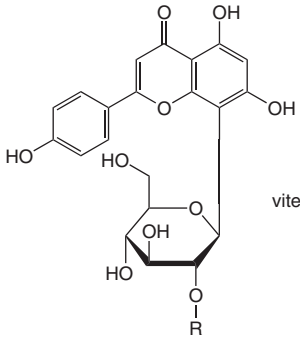
Contains not less than 1.5% of flavonoids, calculated as hyperoside (*1*), and not less than 0.6% of flavone C-glycosides, calculated as vitexin (*14*), determined by spectrophotometry at 410 and 336 nm, respectively (*1*). A high-performance liquid chromatography method is also available (*19*).

Major chemical constituents

The major constituents are flavonoids (rutin, hyperoside, vitexin, vitexin-2″ rhamnoside, acetylvitexin-2″ rhamnoside) and related proanthocyanidins (*19*, *20*). In the inflorescence, flavonol glycosides, mainly in the form of hyperoside, spiraeoside and rutin, are present. The primary flavonoid derivatives in the leaves are *epi*-catechin (*epi*-catechol) and/or catechin (catechol), and the related procyanidins formed during condensation of 2–8 monomeric units of the above catechins (*19–22*), together with oligomeric procyanidins (*23*). The presence of simple phenolic acids (e.g. chlorogenic and caffeic acids) has also been reported. Of the non-phenolic constituents, pentacyclic triterpenes (e.g. ursolic and oleanolic acids) and the 2-α-hydroxy derivative of oleanolic acid, known as crataegolic acid, are among the characteristic components (*4*). The structures of the characteristic constituents are presented below.

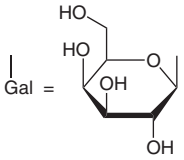


	R	X
hyperoside	H	Gal
spiraeoside	Glc	H
rutin	H	Rha-Glc

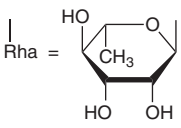


vitexin
R = H

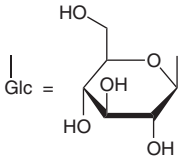
vitexin 2″-rhamnoside
R = Rha



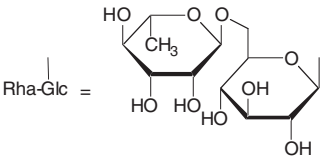
β-D-galactopyranosyl



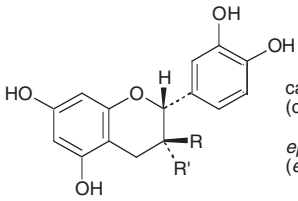
α-L-rhamnopyranosyl =
6-deoxy-α-L-mannopyranosyl



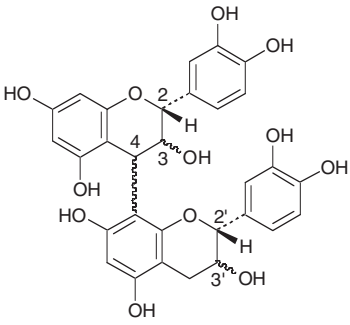
β-D-glucopyranosyl



6-deoxy-α-L-mannopyranosyl-(1→6)-
β-D-glucopyranosyl



	R	R′
catechin (catechol)	OH	H
epi-catechin (*epi*-catechol)	H	OH



procyanidin	2	2′	3	3′	4
B_1	α-(*R*)	α-(*R*)	α-(*R*)	β-(*S*)	β-(*R*)
B_2	α-(*R*)	α-(*R*)	α-(*R*)	α-(*R*)	β-(*R*)
B_3	α-(*R*)	α-(*R*)	β-(*S*)	β-(*S*)	α-(*S*)
B_4	α-(*R*)	α-(*R*)	β-(*S*)	α-(*R*)	α-(*S*)

Medicinal uses

Uses supported by clinical data

Treatment of chronic congestive heart failure stage II, as defined by the New York Heart Association (*24–34*).

Uses described in pharmacopoeias and in traditional systems of medicine

Support of cardiac and circulatory functions (*35*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antispasmodic agent in the treatment of asthma, diarrhoea, gall bladder disease and uterine contractions, and as a sedative for the treatment of insomnia (*5*).

Pharmacology

Experimental pharmacology

Inotropic effects

Positive inotropic effects of Folium cum Flore Crataegi and its constituents have been demonstrated both in vitro and in vivo. These effects are generally attributed to the flavonoid and procyanidin constituents of the leaves with flowers (*3*, *36–38*). A hydroalcoholic extract of the flowers with leaves, flavonoid and procyanidin fractions of the extract, and isolated constituents (e.g. biogenic amines, crataegolic acid, *epi*-catechin, hyperoside, luteolin 7-glucoside, rutin and vitexin) all have positive inotropic effects, and prolong the refractory period in cardiac myocytes, isolated papillary muscles and isolated guinea-pig hearts (*36–48*). In isolated guinea-pig hearts perfused at constant pressure, 3 µg/ml of a standardized extract increased the contractility of the heart by 9.5% (*40*). In isolated, electrically stimulated strips of failing human left ventricular myocardium, a standardized extract (18.75% oligomeric procyanidins) increased the force of contraction at concentrations higher than 10 µg/ml; a 100 µg/ml extract improved the force–frequency relationship (*39*). A standardized extract of the leaves and flowers increased the contractility of myocardial cells by 153%, at a concentration of 120 µg/ml (*44*). An aqueous extract of the leaves with flowers, two proanthocyanidin fractions and two flavonoid fractions of the extract dilated coronary blood vessels, and had positive inotropic effects on isolated guinea-pig hearts (extract or fraction: 0.05 mg/ml) (*41*).

Chronotropic effects

Intragastric administration of a macerate or fluidextract of the shoots, flowers or leaves to rats (12.5–25.0 mg/kg body weight) significantly inhibited arrhythmias induced by aconitine, calcium chloride or chloroform/epinephrine

($P < 0.05$) (*49*, *50*). The extracts also reduced blood pressure in rats at the same dosage (*49*, *50*). Aconitine-induced arrythmias were also inhibited after intravenous administration of a 95% ethanol extract of the bark and leaves (50 mg/kg body weight) to rabbits (*51*). Intravenous administration of a flavonoid-enriched extract of the leaves and flowers to rabbits (20 mg/kg body weight) or rats (2 mg/kg body weight) inhibited barium chloride-induced arrhythmias (*52*, *53*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized dogs (7.5–30.0 mg/kg body weight) increased maximum left ventricular contraction velocity by 16.8–31.1% (*54*).

An aqueous extract improved cardiac performance during reperfusion, reduced lactate levels and accelerated energy metabolism in reperfused ischaemic rat heart. No increase in coronary blood flow was observed (*55*). Intragastric administration of single doses of a standardized extract (containing 18.75% oligomeric procyanidins) of the leaves with flowers (100 mg/kg body weight) or an oligomeric procyanidin-enriched fraction (20 mg/kg body weight) daily to rats protected against perfusion-induced arrhythmias, hypotensive crisis and mortality (*56*, *57*). The oligomeric procyanidin-enriched fraction did not decrease the reperfusion-induced elevation of creatine kinase plasma levels (*57*). Administration of powdered leaves and flowers to rats (2% of diet) reduced the release of lactate dehydrogenase after perfusion-induced heart ischemia (*58*).

Effect on coronary blood flow

Intragastric administration of an oligomeric procyanidin fraction of a standardized leaf and flower extract to dogs at a dose of 12–70 mg/kg body weight, three times daily for 60 days, increased myocardial blood flow (*59*, *60*). Intravenous injection of an aqueous or 95% ethanol extract of the flowers increased coronary blood flow and cardiac output, and decreased peripheral resistance in both dogs and guinea-pigs (*61–63*). Administration of a flavonoid-enriched extract to cats and rabbits increased coronary blood flow by 48% and 163%, respectively, and reduced pituitrin-induced coronary insufficiency in rabbits (*52*). Intravenous administration of a leaf with flower extract to cats (10 mg/kg body weight) or rabbits (20 mg/kg body weight) dilated coronary blood vessels, and improved coronary blood flow (*53*).

Effect on action potential

A leaf preparation (10 mg/l) prolonged the duration of the action potential and delayed the recovery of V_{max} in isolated guinea-pig papillary muscle (*42*). The electrophysiological correlation between the increase in the contraction amplitude of isolated canine papillary muscles, and vasodilation in isolated human coronary arteries, was measured after application of an extract of the leaves with flowers. The cardiac action potential significantly increased in duration and overshoot, and maximal depolarization ($P < 0.001$). Hyperpolarization of

the resting membrane of normal and arteriosclerotic vascular smooth muscle cells of the human coronary artery was observed after treatment with flavonoids isolated from the extract (0.1 and 100 µmol/l). The isometric wall tension decreased in both normal and arteriosclerotic vessels. The increase of peak-to-plateau repolarization in cardiac action potential and hyperpolarization of vascular smooth muscle suggest that the extract acts as a potassium channel agonist (*64*, *65*).

Antihypertensive effects

In various animal models, a decrease in peripheral vascular resistance and hypertension occurred after treatment with leaf and/or flower extracts (*50*, *54*, *66–69*). Intravenous administration of a standardized fluidextract of the leaves with flowers (equivalent to 6 mg of procyanidins/kg body weight) to anaesthetized normotensive dogs decreased norepinephrine-induced elevation of blood pressure. The extract (equivalent to 0.03 mg procyanidins/ml) also had β-blocking activity and inhibited epinephrine-induced tachycardia in isolated frog hearts (*69*). Hyperoside, isolated from an extract of the leaves and flowers, administered either intravenously at a dose of 1 mg/kg body weight or by infusion at 0.1 mg/kg body weight/min for 30 min, decreased blood pressure in anaesthetized dogs (*68*). Intravenous administration of an aqueous extract of the leaves (average dose 31 mg/kg body weight) decreased the systolic, diastolic and mean blood pressure in normotensive anaesthetized rats (*66*). Acute or chronic intragastric administration of a fluidextract or a glycerol/ethanol extract reduced arterial blood pressure in normotensive rats and in rats with desoxycorticosterone acetate-induced hypertension (*50*). Intragastric administration of a standardized extract (300 mg/kg body weight daily) decreased blood pressure by 9 mm Hg (1.20 kPa) (*67*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized rats (30 mg/kg body weight) or dogs (15 mg/kg body weight) decreased total peripheral resistance and arterial blood pressure (*54*).

Anti-inflammatory effects

Both free radical production and lipid peroxidation are involved in various pathological processes, including cardiac ischaemia. As determined by in vitro studies, Folium cum Flore Crataegi has free radical scavenging and antioxidant activities. A standardized extract (containing 18.75% oligomeric procyanidins) and an oligomeric procyanidin-fraction of the extract inhibited lipid peroxidation (IC_{50} 0.48 µg/ml (extract), 0.3 µg/ml (fraction)), and the activity of human neutrophil elastase (IC_{50} 4.75 µg/ml (extract), 0.84 µg/ml (fraction)) (*56*). A 70% methanol extract of the flower buds inhibited lipid peroxidation in rat liver microsomes (IC_{50} 23 mg/l) (*70*, *71*). Both phenolic and flavonoid-enriched fractions of extracts of the leaves and flowers had antioxidant activity in vitro (*70–72*).

Effect on signal transduction

An aqueous or methanol extract of the leaves with flowers, as well as hyperoside, vitexin and vitexin rhamnoside, inhibited the activity of cyclic AMP-dependent phosphodiesterase isolated from guinea-pig or rat heart (*73*, *74*). Both luteolin 7-glucoside and rutin were also active (*75*). Hydroalcoholic extracts of the flowers and flower heads inhibited the formation of thromboxane A_2 and prostaglandin I_2 in rabbit cardiac tissues in vitro, thus indicating an anti-inflammatory effect of the extracts (*76*, *77*). A standardized extract (containing 18.75% oligomeric procyanidins) displaced ^{3}H-ouabain bound to sodium- and potassium-activated adenosine triphosphatase (*39*).

Anticontractile effects

An aqueous extract of the flowers inhibited barium chloride-induced contractions in rabbit intestine in vitro (*78*). A flavonoid-enriched extract of the leaves with flowers inhibited both histamine- and nicotine-induced contractions in rabbit intestine in vitro and partially inhibited contractions induced by barium chloride, acetylcholine or serotonin (ED_{50} 0.02 mg/ml) (*52*). Intravenous administration of a flavonoid-enriched extract of the leaves with flowers to cats (20 mg/kg body weight) inhibited contractions in intestinal smooth muscle, and intraperitoneal injection (400 mg/kg body weight) inhibited acetic acid-induced writhing in mice (*52*).

Sedative effects

Sedative effects have been observed in various animal models after intragastric administration of leaf with flower extracts (*79*, *80*). A 60% ethanol extract of the flowers increased hexobarbital-induced sleeping times, and decreased spontaneous motility and exploratory behaviour in female mice (800 mg/kg body weight) (*80*).

Diuretic effects

A flavonoid-enriched fraction of a flower extract had diuretic activity in dogs (50 mg/kg body weight) (*81*).

Toxicology

Single-dose toxicity studies have demonstrated that rats and mice tolerate 3 g/kg body weight, by gastric lavage, of a standardized hydroalcoholic extract of the leaves with flowers (containing 18.75% oligomeric procyanidins) without any clinical symptoms of toxicity. The intraperitoneal median lethal dose (LD_{50}) was 1.17 g/kg body weight in rats and 750 mg/kg body weight in mice. No toxic effects were observed in a repeat-dose toxicity study in which rats and dogs were given a standardized extract (containing 18.75% oligomeric procyanidins) at doses of 30, 90 and 300 mg/kg body weight daily by the intragastric route for 26 weeks (*82*).

Clinical pharmacology

Cardiac insufficiency

Review of the pharmacological and clinical data indicates that standardized extracts of Folium cum Flore Crataegi increase myocardial performance, improve myocardial circulatory perfusion and tolerance in cases of oxygen deficiency, have antiarrhythmic effects and reduce afterload (*29*). Positive therapeutic effects of Folium cum Flore Crataegi in patients with characteristic symptoms of an activated sympathoadrenergic system, such as hypertension, tachycardia and arrhythmia (also characteristic of cardiac insufficiency stage II, as defined by the New York Heart Association (*25–34*)), have also been demonstrated (*30*). Furthermore, numerous clinical trials with and without controls have assessed the therapeutic efficacy of Folium cum Flore Crataegi extracts for the treatment of cardiac insufficiency stage II (*25–34*). The investigations were performed with a dried 70% methanol or 45% ethanol standardized extract (containing 2.2% flavonoids or 18.75% oligomeric procyanidins, respectively) of the leaves with flowers (*30*). The dosage ranged from 160 to 900 mg extract daily for 4–8 weeks. Evaluation of efficacy of the extracts was based on the following criteria: anaerobic threshold (*27*); Clinical Global Impression Scale (*31*, *32*); exercise tolerance (*25*, *26*, *28*, *31*, *32*, *34*); ventricular ejection fraction (*26*, *33*); quality of life and improvement of subjective symptoms (defined by the New York Heart Association) (*26–28*, *31–34*) and pressure/rate product (*26*, *28*, *31*, *32*, *34*). Although improvements were seen, no long-term trials have assessed the effects of Folium Cum Flore Crataegi on mortality rates in patients with chronic congestive heart failure.

Exercise tolerance

A randomized, double-blind, placebo-controlled trial assessed the efficacy of the extract containing 2.2% flavonoids on exercise-induced anaerobic threshold, as measured by spiroergometry, in 72 patients. Patients were administered an oral dose of 900 mg extract or placebo daily for 8 weeks. After treatment, oxygen uptake increased significantly in the treated group ($P < 0.05$), and exercise time to anaerobic threshold increased by 30 seconds in the treated group, but by only 2 seconds in the placebo group. Significant improvements in subjective symptoms were also noted in the treated group, as compared with the placebo group ($P < 0.01$) (*27*).

The efficacy of the extract containing 2.2% flavonoids on the improvement of exercise tolerance was assessed by bicycle ergometry in patients with cardiac insufficiency stage II, in three clinical trials. In a double-blind, placebo-controlled trial of 85 patients, oral administration of 300 mg extract daily for 4–8 weeks improved working capacity; however, the difference was not significant when compared with the placebo (*25*). A double-blind, placebo-controlled trial assessed the efficacy of oral administration of 600 mg extract daily for 8 weeks in 78 patients. Patients in the treatment group had a significant improvement in exercise tolerance as compared with the placebo group

($P < 0.001$). Patients who received the extract also had lower blood pressure and heart rate during exercise, and had fewer overall symptoms, such as dyspnoea and fatigue (*31*). In the third trial, 132 patients were treated orally with 900 mg extract or 37.5 mg captopril daily for 8 weeks in a double-blind comparative study. Exercise tolerance, measured after 56 days of treatment, improved significantly in both groups ($P < 0.001$). In addition, the pressure/rate product was reduced, and the incidence and severity of symptoms such as dyspnoea and fatigue decreased by approximately 50% (*32*).

Pressure/rate product

Two double-blind, placebo-controlled trials assessed the efficacy of the extract containing 18.75% oligomeric procyanidins in a total of 156 patients with stage II cardiac insufficiency. Patients were treated orally with 160 mg extract or placebo daily for 8 weeks. The main parameters measured were the pressure/rate product using a bicycle ergometer, and the score of subjective symptom status. Patients treated with the extract exhibited a significant improvement in exercise tolerance, as compared with the placebo group ($P < 0.05$), and also a decrease in subjective complaints (*28*, *34*). In addition, a slight reduction in the systolic and diastolic blood pressure was noted in both groups (*28*).

Ventricular ejection fraction

In a trial without controls involving seven patients with stages II and III cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, oral administration of 240 mg extract containing 18.75% oligomeric procyanidins daily for 4 weeks increased the ventricular ejection fraction from 29.80 to 40.45%, as measured by angiography. Symptomatic complaints (Complaint List as defined by von Zerssen) also showed improvements (*33*). The effects of the extract containing 18.75% oligomeric procyanidins on haemodynamics were also investigated by radionuclide angiocardiography in a study without controls. Twenty patients with stage II cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, were treated with 480 mg extract. After treatment, the ejection fraction increased from 40.18 to 43.50% at rest, and from 41.51 to 46.56% under exercise conditions. Ergometric tolerance to exercise improved, blood pressure decreased and subjective complaints were reduced (*26*).

Pharmacokinetics

Absorption of a ^{14}C-labelled oligomeric procyanidin fraction of standardized extracts of leaves with flowers was measured in mice after intragastric administration (0.6 mg). The results demonstrated that 20–30% of the total fraction, 40–81% of the trimeric procyanidins and 16–42% of the oligomeric procyani-

dins were absorbed within 1–7 hours after administration. After 7 hours, 0.6% of the radioactivity of the total fraction was eliminated by expiration and 6.4% was eliminated in the urine. Daily intragastric administration of 0.6 mg of a radiolabelled oligomeric procyanidin fraction to mice for 7 days led to an accumulation of radioactivity that was 2–3 times that in mice given a single dose (*83*).

Contraindications

None (*84*).

Warnings

Accurate diagnosis of stage II congestive heart failure should be obtained prior to use of Folium cum Flore Crataegi. Consult a physician if symptoms worsen, remain unchanged for longer than 6 weeks, or if water accumulates in the legs. Medical attention is absolutely necessary if pain occurs in the region of the heart, spreading out to the arms, upper abdomen or neck area, or in cases of respiratory distress (e.g. dyspnoea) (*84*).

Precautions

Drug interactions

None (*84*).

Drug and laboratory test interactions

No effects in laboratory tests (i.e. serum levels of sodium chloride, potassium chloride, calcium chloride, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, γ-glutamyl transpeptidase, total bilirubin, cholesterol and creatinin, and blood glucose levels) were observed (*34*).

Carcinogenesis, mutagenesis, impairment of fertility

A standardized extract of Folium cum Flore Crataegi (containing 18.75% oligomeric procyanidins) was not mutagenic or clastogenic in the *Salmonella*/microsome assay, mouse lymphoma test, cytogenetic analysis in cultured human lymphocytes or in the mouse bone marrow micronucleus test (*82*). A fluidextract was moderately active in the *Salmonella*/microsome assay in *S. typhimurium* strain TA98 only after metabolic activation. The mutagenic activity appeared to be due to the quercetin content of the extract; however, the amount of quercetin ingested in a normal daily diet is higher than would be obtained from the extract (*85*). Intragastric administration of up to 1.6 g/kg body weight had no effect on the fertility of female and male rats or the F_1 generation (*86*).

Pregnancy: teratogenic effects

Intragastric administration of up to 1.6 g/kg body weight of a standardized extract of Folium cum Flore Crataegi to rats and rabbits was not teratogenic (*86*).

Pregnancy: non-teratogenic effects

No peri- or postnatal toxicity was observed in rats treated intragastrically with a standardized extract of Folium cum Flore Crataegi (1.6 g/kg body weight) (*86*).

Other precautions

No information available on general precautions or precautions concerning nursing mothers or paediatric use. Therefore, Folium cum Flore Crataegi should not be administered during lactation or to children without medical supervision.

Adverse reactions

None (*84*).

Dosage forms

Crude drug for infusion and hydroalcoholic extracts (*35*). Store in a well-closed container, protected from light and moisture (*1*).

Posology

(Unless otherwise indicated)
Daily dosage: 160–900 mg dried 45% ethanol or 70% methanol extract (drug: extract ratio 4–7 : 1) standardized to contain 18.75% oligomeric procyanidins (calculated as *epi*-catechin) or 2.2% flavonoids (calculated as hyperoside), respectively (*26–29*, *31–34*, *84*); 1.0–1.5 g comminuted crude drug as an infusion 3–4 times daily (*35*). Therapeutic effects may require 4–6 weeks of continuous therapy (*84*).

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Radix Eleutherococci

Definition

Radix Eleutherococci consists of the dried roots and rhizomes of *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim. (Araliaceae) (*1*–*3*).[1]

Synonyms

Acanthopanax senticosus (Rupr. et Maxim.) Harms., *Hedera senticosa* (*1*, *4*, *6*).

Selected vernacular names

Buisson du diable, chi wu cha, ciwujia, devil's bush, devil's shrub, eleuthero, eleutherococc, eleutherococoque, eleutherokokk koljucij, ezoukogi, gashi ohgap, hongmao-wujiapi, many prickle acanthopanax, pai wu cha pi, prickly eleutherococc, prickly eleutherococcus, shigoka, Siberian ginseng, Stachelkraftwurz, Stachelpanax, taiga root, Taigawurzel, thorny ginseng, thorny Russian pepperbush, touch-me-not, tsu wu cha, wild pepper, wu cha sang, wu cha seng, wu jia pi (*2*, *7*).

Geographical distribution

Indigenous to south-east Asia, northern China, the Democratic People's Republic of Korea, Japan and the south-eastern part of the Russian Federation (*4*, *5*).

Description

A prickly shrub, up to 4–6 m high, usually with several mostly unbranched stems; oldest stems may be unarmed, while the youngest are densely covered with flexible prickles. Palmate leaves, on long, often reddish stalks, usually composed of 5 elliptical leaflets with serrate margins. Flowers small, polygamous, occurring toward the tips of stems in single or paired umbels that have long peduncles. Floral parts are in groups of 5, including the epigynous ovary surrounded by a nectar-secreting disc. Fruit, a drupe, contains the same number of kernels as carpels. Flower and fruit resemble those of ivy (*Hedera helix*) (*8*).

[1] A 33% ethanol extract of Radix Eleutherococci is listed as Extractum Radicis et Rhizomatis Eleutherococcus in the Russian Pharmacopoeia (*4*, *5*).

Plant material of interest: dried roots and rhizomes

Roots from the unrelated plant *Periploca sepium* Bunge (Asclepiadaceae) (Chinese silk vine) have been surreptitiously used as a substitute for Radix Eleutherococci in commerce. To a lesser extent, roots from the related *Acanthopanax* species and *Kalopanax septemlobus* (Thunb.) Koidz. (Araliaceae) have also been so used (*9, 10*).

General appearance

Roots: cylindrical, up to 0.5 cm in diameter, straight, occasionally branched, dark brown, smooth surface with bark adhering closely to the xylem. Rhizomes: up to 4 cm thick, pale brown, longitudinally wrinkled, showing root scars and traces of aerial stems; fracture somewhat fibrous; fractured surface pale yellow (*1*).

Organoleptic properties

Odour: faint, aromatic; taste: bitter, acrid, persistent (*1*).

Microscopic characteristics

Roots: rows (5–7) of brown cork cells; secondary phloem containing secretory canals in groups of 4 or 5, up to 20 µm in diameter, with brown contents; phloem fibres with thick, lignified walls occurring singly or in small groups; cluster crystals of calcium oxalate in phloem parenchyma; parenchymatous cells surrounding secretory cells and the medullary ray cells containing small starch grains; xylem of reticulate and bordered, pitted vessels. Rhizomes: similar to the roots except for larger secretory canals, up to 25 µm in diameter, and presence of parenchymatous pith containing starch grains (*1*).

Powdered plant material

Yellowish; numerous groups of thick-walled, lignified fibres; fragments of reticulate and bordered, pitted vessels with a wide lumen; groups of secretory canals, up to 20 µm in diameter, with brown contents; parenchymatous cells containing cluster crystals of calcium oxalate 10–50 µm in diameter; small starch grains, rounded to slightly angular in outline, single or in groups of 2 or 3 (*3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), thin-layer chromatography (*2, 3*) and high-performance liquid chromatography (*11–13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 3% (3). Must be free of *Periploca sepium* and other foreign plant materials.

Total ash

Not more than 6% (*1*).

Acid-insoluble ash

Not more than 1.5% (*1*).

Water-soluble extractive

Not less than 4% (*1*).

Alcohol-soluble extractive

Not less than 6% using 75% ethanol (3).

Loss on drying

Not more than 10% (3).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

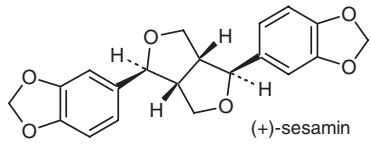
Chemical tests to be established in accordance with national requirements.

Chemical assays

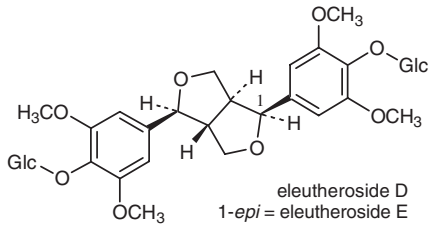
Several methods based on high-performance liquid chromatography are available for quantitative determination of syringaresinol-diglucoside (eleutheroside E) and syringin (eleutheroside B) (*11–13*).

Major chemical constituents

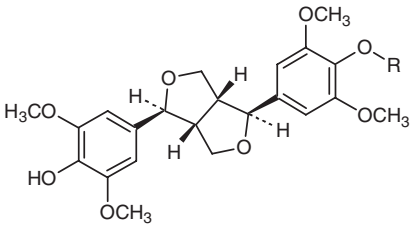
The constituents responsible for the characteristic biological effects of Radix Eleutherococci appear to be a complex mixture of phenylpropane derivatives of diverse structure, and various sugar polymers (*4*, *6*, *11*). The principal components of the former group are the lignans, (+)-sesamin (eleutheroside B_4), (+)-syringaresinol and its monoglucoside (eleutheroside E_1) and diglucoside (eleutherosides D and E); the simple phenylpropanes, syringenin and its monoglucoside (eleutheroside B); and the coumarins isofraxidin and its monoglucoside (eleutheroside B_1). An immunostimulant polysaccharide complex and a glycan series (eleutherans A–G) have also been isolated from the drug (*17*). β-Sitosterol and daucosterol (eleutheroside A) are the major sterols. Eleutheroside E has been found in all samples regardless of geographical origin, whereas eleutheroside B is present in all samples, except those from plants grown in the Democratic People's Republic of Korea (*11*, *12*). The structures of the representative constituents are presented below.



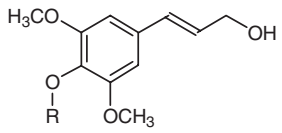
(+)-sesamin



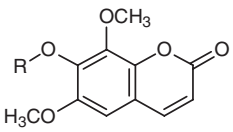
eleutheroside D
1-*epi* = eleutheroside E



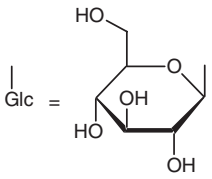
(+)-syringaresinol R = H
eleutheroside E_1 R = Glc



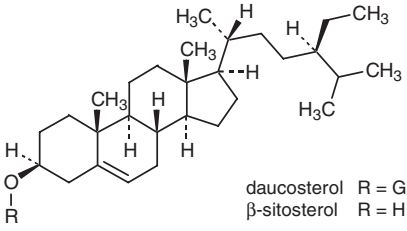
syringenin R = H
eleutheroside B R = Glc



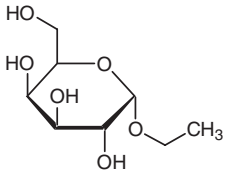
isofraxidin R = H
eleutheroside B_1 R = Glc



β-D-glucopyranosyl



daucosterol R = Glc
β-sitosterol R = H



eleutheroside C

Medicinal uses

Uses supported by clinical data

As a prophylactic and restorative tonic for enhancement of mental and physical capacities in cases of weakness, exhaustion and tiredness, and during convalescence (*4*, *18–20*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of rheumatoid arthritis, insomnia and dream-disturbed sleep (*2*).

Uses described in folk medicine, not supported by experimental or clinical data

As a carminative in the treatment of acute and chronic gastritis, as a diuretic, to treat impotence and to regulate blood pressure (*7*).

Pharmacology

Experimental pharmacology

Adaptogenic/antistress activity

The mechanism of the antistress or adaptogenic activities of Radix Eleutherococci appears to be threefold. Extracts of the roots have an adaptogenic effect that produces a non-specific increase in the body's defence against exogenous stress factors and noxious chemicals (*4*, *21*, *22*). The roots also stimulate the immune system, and promote an overall improvement in physical and mental performance (*4*).

Numerous in vivo studies have demonstrated the pharmacological activity of a 33% ethanol extract of the roots in a variety of animal models (*4*, *23–29*). Most of these investigations were designed to analyse the adaptogenic response to a variety of adverse conditions (stress, immobilization or chemical challenge) (*4*, *24*, *25*, *28*, *30*). An increase in the resistance of rats to the toxic effects of noxious chemicals such as alloxan, cyclophosphan, ethymidine and benzo-tepa was observed after oral administration of a 33% ethanol extract of the roots (1–5 ml/kg body weight) (*24*, *25*, *28*). Intragastric administration of a 33% ethanol extract of the roots to mice (10 ml/kg body weight) decreased the toxicity of diethylglycolic acid, but did not reduce the severity of electroshock-induced convulsions (*31*). Administration of a 10% decoction of the roots to frogs' ventral lymph sac (0.1 ml) protected them against injection of lethal doses of cardiac glycosides (*32*). Intragastric administration of a 33% ethanol extract of the roots (1.0 ml/kg body weight) daily for 21–23 days increased the resistance of rats to the toxic effects of alloxan, but did not lower alloxan-induced hyperglycaemia (*33*). Intragastric administration of a freeze-dried extract of the roots (80 or 320 mg/kg body weight) daily for 3 days decreased blood glucose levels of mice by 35% and 60%, respectively, compared with placebo treat-

ment (*34*). Reduction of blood glucose levels may be due partially to enhanced synthesis of glycogen and high-energy phosphate compounds (*35*).

Investigations to elucidate the adaptogenic effect on the lymphatic system assessed the ability of root extracts to inhibit cortisone-induced weight decreases of the thymus and spleen in rats (*4*). Intraperitoneal administration of a 33% ethanol extract of the roots (1.0 ml/kg body weight) daily for 8 days prevented a decrease in spleen and thymus weight due to cortisone administration (*22*). A 33% ethanol root extract had normalizing effects on experimentally induced hypothermia when administered intragastrically to rats and mice (0.1 or 1.0 ml/kg body weight) daily for 12–14 days (*36*). Intragastric administration of a 33% ethanol extract of the roots to rats and mice normalized experimentally induced hypothermia, and acted as a sedative (*37*).

Intragastric administration of an aqueous extract of the roots to mice (500 mg/kg body weight) decreased stress-induced enlargement of the adrenal gland, normalized a decrease in rectal temperature due to chronic stress, and enhanced sexual behaviour (*26*). Intragastric administration of an aqueous extract of the roots (500 mg/kg body weight) daily for 15 days prolonged the swimming times of rats (*38*). Intragastric administration of an aqueous or butanol extract of the roots to rats (500 mg/kg body weight) suppressed gastric ulcer formation induced by stress (immersion in cold water) (*39*). Intragastric administration of an aqueous extract of the roots (500 mg/kg body weight) to rats suppressed the decrease in locomotor activity induced by exposure to light, indicating a reduction in the anxiety levels of the animals (*40*).

The antistress or adaptogenic effects of Radix Eleutherococci are produced through metabolic regulation of energy, nucleic acids and proteins of the tissues. Under stress, a β-lipoprotein–glucocorticoid complex is generated in the blood. This complex inhibits permeation of cell membranes by sugars and also inhibits hexokinase activity in vivo and in vitro (*4*). The root extracts increase the formation of glucose-6-phosphate, which in turn decreases the competition between the different pathways of its utilization. In animal tissues deficient in ATP, glucose-6-phosphate is oxidized via the pentose phosphate pathway, yielding substrates for the biosynthesis of nucleic acids and proteins (*4*). The constituents syringin (eleutheroside B) and (–)-syringaresinol-4,4′-*O*-β-D-diglucoside (eleutheroside E) are thought to be responsible for the adaptogenic activity (*21*). Intraperitoneal administration of total eleutherosides isolated from the roots to rats (5.0 mg/kg body weight) partially reversed the decrease in the levels of muscle ATP, glycogen, creatine phosphate, lactic acid and pyruvic acid induced by 2 hours of swimming. The same treatment also increased the work capacity of mice (*41*). Intraperitoneal administration of total eleutherosides to rats (15 mg/kg body weight), 1 hour prior to 15 minutes of forced swimming, delayed the inhibition of RNA polymerase. The same treatment also increased the activity of this enzyme during rest periods (*42*). Intragastric administration of a butanol extract of the roots to mice (170 mg/kg body weight, daily, 6 days a week for 6 weeks) enhanced the activities of oxidative enzymes and superoxide dismutase in skeletal muscle, resulting in improved aerobic metabolic

rates (*43*). Intragastric administration of an aqueous extract of the roots to mice (170 mg/kg body weight, daily for 9 weeks) increased the activity of succinate dehydrogenase and malate dehydrogenase in skeletal muscle (*44*).

Intraperitoneal administration of an aqueous root extract to mice (40–320 mg/kg body weight) increased sleeping times up to 228% compared to controls treated with hexobarbital, and decreased sleep latency when given in conjunction with hexobarbital (*45*).

Intraperitoneal administration of an aqueous extract of the roots to rats (3 mg/kg body weight) caused a significant increase in corticosterone levels 3 hours after injection, whereas adrenocorticotropic hormone levels remained unchanged (*40*). Intraperitoneal administration of a fluidextract of the roots (1.0 ml/kg body weight) increased anabolic activity in male rats (*46*). Oral administration of a glycoside fraction isolated from an ethanol root extract to rats (5.0 mg/kg body weight) increased the body weight and RNA content of the prostate and seminal vesicles, and inhibited atrophy of the prostate and seminal vesicles in castrated animals (*47*). A 30% ethanol extract of the roots was shown to bind in vitro to the estrogen receptor in rat uterus, and the glucocorticoid and mineralocorticoid receptors in rat kidney, but not to the androgen receptor in rat kidney (*48*).

Antimicrobial activity

Parenteral administration of a 33% ethanol extract of the roots (dose not specified) increased the resistance of mice and rabbits to listeriosis when administered for 15 days prior to infection (*49, 50*). However, administration of the extract simultaneously with the bacteria increased the severity of the infection (*49*). Intragastric administration of the same extract (1 ml daily) for 15 days stimulated specific antiviral immunity in guinea-pigs and mice (*51*). A polysaccharide fraction of the roots (0.01 mg/ml) increased the activities of lymphokine-activated killer (LAK) cells and enhanced the activities of interleukin 2-stimulated LAK cells in vitro (*52*). A 95% ethanol extract of the roots (1 ml daily) increased phagocytosis of *Candida albicans* by human granulocytes and monocytes in vitro by 30–45% (*53*). Intraperitoneal administration of a polysaccharide fraction isolated from an aqueous root extract (10 mg/kg body weight) had immunostimulant activity in mice, as demonstrated by the colloidal carbon clearance test (*17*). A pyrogen-free polysaccharide fraction of the roots stimulated lymphocyte phagocytosis and T-cell-dependent functions of B-cells in vitro, as determined by plaque-forming cell stimulation assays and the production of anti-bovine serum albumin antibodies. Intraperitoneal administration of the same polysaccharide fraction to mice (100 mg/kg body weight daily for 7 days) significantly increased plaque-forming cell counts, anti-bovine serum albumin antibody levels and the phagocytic activity of lymphocytes (*54*). Intraperitoneal administration of a polysaccharide fraction of an aqueous extract of the roots to mice (125 mg/kg body weight) markedly increased the serum levels of anti-bovine serum albumin IgA and total anti-bovine serum albumin immunoglobulins, but not total IgA (*55*).

Inhibition of platelet aggregation

A 100% methanol extract of the root inhibited ADP-induced platelet aggregation in blood samples from rats and humans in vitro (*56*).

Clinical pharmacology

Adaptogenic/antistress activity

Numerous clinical studies, designed to measure the adaptogenic effects of Radix Eleutherococci, were performed in Russia during the 1960s and 1970s (reviewed in Farnsworth et al., 1985 [*4*]). In 35 clinical trials without controls, involving over 2100 healthy subjects (4–1000 per study), oral administration of a 33% ethanol root extract (2.0–20.0 ml, daily for up to 60 days) improved physical and mental work performance under stress conditions, and reduced auditory disorders and the incidence of illness (*4*, *30*).

In another 35 clinical trials without controls, the effects of a 33% ethanol extract of the roots were assessed in 2200 patients (5–1200 per study) with various disorders, such as arteriosclerosis, acute pyelonephritis, diabetes, hypertension, hypotension, chronic bronchitis and rheumatic heart disease. Patients received 0.5–6.0 ml extract orally 1–3 times daily for up to eight courses of 35 days each, each course being separated by 2–3 weeks without treatment. The overall results were generally positive: for example, blood pressure was normalized, serum prothrombin and cholesterol levels were reduced, and overall well-being and physical work performance improved (*4*). It should be noted, however, that these trials lacked good methodology (for example, they used only a small number of patients, lacked proper controls and randomization, and were not double-blind).

A single-blind, placebo-controlled clinical trial in six baseball players assessed the effects of a 33% ethanol root extract on maximal work capacity. Three maximal work tests using a bicycle ergometer were performed on 3 consecutive days prior to treatment, and two tests were carried out after treatment with either 2 ml extract (containing 0.53 mg syringin (eleutheroside B) and 0.12 mg syringaresinol-4,-4′-*O*-β-diglucoside (identified here as eleutheroside D)) or placebo orally twice daily for 8 days. After each work test, maximal oxygen uptake, oxygen pulse, total work time and exhaustion time were measured. A significant improvement in all four parameters was observed in subjects treated with the extract ($P < 0.01$), including a 23.3% increase in total work time as compared with only a 7.5% increase following placebo treatment (*18*). A randomized, double-blind, placebo-controlled study measured the effect of an ethanol extract of the roots (standardized to contain 0.2% w/v syringin) on the immune system, using quantitative multiparameter flow cytometry with monoclonal antibodies directed against specific surface markers of human lymphocyte subsets to determine cellular immune status. Thirty-six healthy subjects were treated orally with either 10 ml extract or placebo three times daily for 4 weeks. Subjects treated with the extract had a significant increase in the total number of immunocompetent cells ($P < 0.0001$), including lymphocytes

(predominantly T-cells, T-helper/inducer cells and natural killer cells). A significant increase in activated T-cells was also observed ($P < 0.01$) (*19*). A randomized, double-blind, placebo-controlled study examined the effect of the crude drug on submaximal and maximal exercise performance. Twenty highly trained distance runners received either a 30–34% ethanol extract of the roots (3.4 ml) or placebo daily for 8 weeks, during which they completed five trials of both 10 minute and maximal treadmill tests. Heart rate, oxygen consumption, expired minute volume, ventilatory equivalent for oxygen, respiratory exchange ratio and rating of perceived exertion were measured during both tests. Serum lactate levels were analysed in blood samples. No significant differences were observed in any of the measured parameters between the placebo and treatment groups (*57*). A randomized, placebo-controlled, crossover study of 30 healthy volunteers compared the effects of Radix Eleutherococci, *Panax ginseng* and placebo on maximal oxygen uptake, using a bicycle ergometer. After 6 weeks of treatment, maximal oxygen uptake increased significantly only in subjects who had received *P. ginseng* (*58*). A comparative study assessed the ability of tinctures of Radix Eleutherococci and *Leuzea carthamoides* (containing eleutherosides and ecdysones, respectively) to decrease blood coagulation in highly trained athletes. Athletes treated with a 20-day course of the Radix Eleutherococci tincture showed a decrease in blood coagulation, and the activity of blood coagulation factors induced by intensive training (*59*).

Contraindications

Radix Eleutherococci should not be used during pregnancy or lactation, or by patients with blood pressure in excess of 180/90 mmHg (24/12 kPa) (*4*). Radix Eleutherococci is also contraindicated in cases of known allergy to plants of the Araliaceae family.

Warnings

No information available.

Precautions

Drug interactions

There is one case report of an increased level of serum digoxin due to the concomitant use of digoxin and Radix Eleutherococci (*60*). However, the identity of the plant material as *Eleutherococcus senticosus* was not established, and it is believed that it may have been *Periploca sepium*, which contains cardiac glycosides (*9*, *10*).

Carcinogenesis, mutagenesis, impairment of fertility

No carcinogenicity was observed in rats (*61*). No mutagenic activities were observed in the *Salmonella*/microsome assay using *S. typhimurium* strains TA100

and TA98, in the mouse bone marrow micronucleus test, or in rats in vivo (*61*). Desmutagenic effects were observed in *Drosophila* (*62*, *63*).

Pregnancy: teratogenic effects

No teratogenic effects were observed in the offspring of rats administered total eleutherosides intragastrically (10 mg/kg body weight) daily for 16 days, or in pregnant rats given 13.5 ml/kg body weight fluidextract of Radix Eleutherococci daily during days 6–15 of gestation (*64*, *65*). No teratogenic effects were observed in the offspring of sheep or mink when an ethanol extract of the roots was added to the diet (*4*). (See also Contraindications.)

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions or paediatric use. Therefore, Radix Eleutherococci should not be used in children without medical supervision.

Adverse reactions

A few cases of insomnia, arrhythmia (including tachycardia), extrasystole and hypertonia were reported in a clinical study involving 64 patients with atherosclerosis, who received a 33% ethanol extract of the crude drug at a dose of 4.5–6.0 ml daily for 6–8 cycles of treatment (lasting 25–35 days) (*66*). In another study of 55 patients with rheumatic heart lesions, two patients experienced hypertension, pericardial pain and palpitations, and pressure headaches after ingesting 3 ml of a 33% ethanol extract of the roots daily for 28 days (*67*). Insomnia has also been reported as a side-effect in other clinical trials (*4*). In one case report, neonatal androgenization was tentatively associated with the ingestion of Radix Eleutherococci tablets during pregnancy (*68*, *69*). However, analysis of the raw materials used in the preparation of the tablets indicated that they were probably from *Periploca sepium* (*70*). Furthermore, intragastric administration of either Radix Eleutherococci or *P. sepium* to rats (1.5 g/kg body weight) did not demonstrate any androgenization potential, indicating that the neonatal androgenization was probably not due to the plant material (*71*).

Dosage forms

Powdered crude drug or extracts in capsules, tablets, teas, syrups, fluidextracts (*63*). Store in a well-closed container, protected from light (*3*).

Posology

(Unless otherwise indicated)
Daily dosage: 2–3 g powdered crude drug or equivalent preparations (*20*).

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Aetheroleum Eucalypti

Definition

Aetheroleum Eucalypti is the essential oil obtained by steam distillation and rectification of the fresh leaves or terminal branchlets of *Eucalyptus globulus* Labill (Myrtaceae) or other *Eucalyptus* species rich in 1,8-cineole (*1–3*).

Synonyms

Eucalyptus cordata Miq., *E. diversifolia* Miq., *E. gigantea* Dehnh., *E. glauca* D.C., *E. globulus* St Lag., *E. pulverulenta* Link (*4*).

Selected vernacular names

Aceite de eucalipto, esencia de eucalipto, essence d'eucalyptus rectifiée, eucalipto essenza, eucalyptus oil, eucalyptus olie, Eucalyptusöl, huile essentielle d'eucalyptus, klei de eucalipt, minyak ekaliptus, oleo de eucalipto, Oleum eucalypti, tinh dâu Bach dan (*1–7*).

Geographical distribution

Indigenous to Australia, cultivated in subtropical regions of the world including Africa, South America (e.g. Argentina, Brazil and Paraguay), Asia (e.g. China, India and Indonesia), southern Europe and the United States of America (*4, 7–11*).

Description

A large tree with smooth bark, very pale or ash-grey, up to 3–20 m high. Branchlets quadrangular, glaucous. Leaves of young trees and first leaves of young shoots opposite, sessile, oval-oblong, with a cordate base, farinaceous-glaucous; older leaves dangling, spirally arranged, lanceolate-falcate, up to 30 cm long. Flowers with very short pedicels, mostly umbellate, sometimes 2–3 in a fascicle. Calyx-tube double: outer tube drops early, smooth, inner tube semi-persistent and warty. Stamens about 1.5 cm long; fruit turbinate, angular, 2.0–2.5 cm in diameter (*12, 13*).

Plant material of interest: essential oil

General appearance

A colourless or pale yellow liquid that darkens slightly on long storage (*1*, *2*).

Organoleptic properties

Odour: aromatic, camphoric; taste: pungent, camphoric, followed by a sensation of cold (*1*–*3*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Thin-layer and gas chromatography (*1*–*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Chemical

Refractive index: 1.458–1.470 (*1*–*3*); specific gravity: 0.906–0.925 (*2*); optical rotation: 0° to +10° (*2*); solubility in ethanol: soluble in 5 volumes of 70% ethanol (*2*, *5*). Methods to detect the presence of aldehyde and phellendrene are available (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

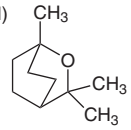
Chemical assays

Contains not less than 70% (w/w) 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1*, *2*). Quantitative analysis according to the method described for 1,8-cineole (*1*–*3*).

Major chemical constituents

The major constituent is 1,8-cineole (54–95%). In addition, there are moderate amounts of α-pinene (2.6%), *p*-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol (*11*, *13*). The structure of 1,8-cineole is presented below.

1,8-cineole (eucalyptol)



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Symptomatic treatment of catarrh and coughs (*17, 18*). As a component of certain dental root canal sealers; topically as a rubefacient for treatment of rheumatic complaints (*18*, *19*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), neuralgia, laryngitis, leukorrhoea, malaria, pimples, ringworm, sinusitis, wounds, ulcers of the skin, urethritis and vaginitis (*4*, *6*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Aetheroleum Eucalypti inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia coli* (*20*–*25*), but not of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (*22*, *25*). Intramuscular injection of the essential oil (500 mg/kg body weight) inhibited the growth of *Mycobacterium tuberculosis* in guinea-pigs, and enhanced the efficacy of streptomycin and isoniazid (*26*).

Anti-inflammatory activity

The essential oil inhibited prostaglandin biosynthesis in vitro at a concentration of 37 µmol/l (*27*).

Respiratory tract effects

Intragastric administration of the essential oil increased respiratory tract secretions in cats (100 mg/kg body weight), guinea-pigs (50 mg/kg body weight), rabbits (100 mg/kg body weight) and rats (100 mg/kg body weight) (*28*). Administration of non-lethal doses of the essential oil by steam inhalation to urethane-treated rabbits did not enhance the output of respiratory tract fluid (*29*).

Antitussive effects

The antitussive effect of the essential oil was compared to that of codeine in guinea-pigs in which coughs were induced by mechanical stimulation. Inhalation of the essential oil (5% emulsified in normal saline) had a significant antitussive effect relative to codeine (15 mg/kg body weight) of 0.68 ($P < 0.05$). When the essential oil was administered by intraperitoneal injection (50 mg/kg body weight), the antitussive effect relative to codeine was 0.57, which was also significant ($P < 0.001$) (*30*).

Clinical pharmacology

Nasal decongestant activity

A clinical trial without controls assessed the effects of Aetheroleum Eucalypti as a nasal decongestant in 31 healthy volunteers. Inhalation of the essential oil (10 ml) over a period of 5 minutes had no effect on nasal resistance to airflow. However, the oil had a stimulant or sensitizing effect on nasal cold receptors, and the majority of subjects reported a sensation of increased airflow (*31*). A single-blind, parallel clinical trial assessed the efficacy of vaporized essential oil, camphor, menthol or steam in reducing nasal congestion in 234 patients with acute respiratory tract infections. The essential oil was significantly more effective in reducing nasal congestion only during the first hour following treatment ($P < 0.02$) (*32*). In other clinical studies of patients with acute common colds, no significant differences in nasal decongestant activity were reported between the essential oil (1.3%) in petrolatum and a petrolatum placebo (*32*).

Analgesic activity

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (eucalyptus oil) and Aetheroleum Menthae Piperitae (peppermint oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; traces of both peppermint oil and eucalyptus oil; or a placebo. The test

preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. All test preparations improved cognitive performance, and induced muscle and mental relaxation compared to the placebo, but had no effect on sensitivity to headache (*33*).

Contraindications

Preparations of Aetheroleum Eucalypti should not be administered internally to children (*34*), or patients with inflammation of the gastrointestinal tract, gall bladder disease or impaired liver function (*4*, *17*, *34*). Aetheroleum Eucalypti should not be taken internally during pregnancy (*35*), see Precautions.

Warnings

Aetheroleum Eucalypti preparations should not be applied to the face, especially the nose, of infants or young children (*17*). Keep out of reach of children.

Precautions

General

Oily vehicles for the essential oil are unsuitable for use in nasal sprays as the vehicle inhibits ciliary movement and may cause lipid pneumonia (*19*).

Drug interactions

Although no published drug interactions were found, a number of animal studies indicate possible concern that the essential oil may induce liver enzymes involved in drug metabolism. Therefore, the effects of other drugs may be decreased following concomitant administration (*17*, *36*).

Carcinogenesis, mutagenesis, impairment of fertility

The essential oil was a weak promoter of papilloma formation by 9, 10-dimethyl-12-benzanthracene in mice. However, the development of tumours in mice after intragastric administration of 8 or 32 mg 1,8-cineole per kg body weight daily for 80 weeks was similar to that in mice treated with vehicle controls (*37*).

Pregnancy: teratogenic effects

The essential oil was not teratogenic when administered subcutaneously to pregnant mice (135 mg/kg body weight) daily on days 6–15 of gestation (*38*).

Pregnancy: non-teratogenic effects

Eucalyptol (500 mg/kg body weight, administered subcutaneously) has been reported to penetrate the placenta in rodents and reach concentrations in the

fetal blood which are sufficient to stimulate hepatic enzyme activity (*39*). Therefore, Aetheroleum Eucalypti should not be taken internally during pregnancy (*35*).

Paediatric use

See Contraindications and Warnings.

Other precautions

No information available on precautions concerning drug and laboratory test interactions or nursing mothers. Therefore, Aetheroleum Eucalypti should not be administered during lactation without medical supervision.

Adverse reactions

Topical applications of Aetheroleum Eucalypti are generally non-irritating, non-sensitizing and non-phototoxic (*40*). However, one case of systemic toxicity in a 6-year-old girl (*41*), and several cases of urticaria, contact dermatitis and skin irritation (*42*) have been reported.

Between 1981 and 1992, the clinical effects of poisoning were observed in 59% of 109 children after accidental ingestion of the essential oil (2–10 ml) (*43*, *44*). The symptoms included depression of conscious state (28% of cases), drowsiness (25% of cases) and unconsciousness (3% of cases), and were dose-dependent (*43*). Other reported symptoms included epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, a feeling of suffocation, cyanosis, delirium and convulsions (*8*, *18*, *45*). Allergic reactions have been reported after ingestion of 20 lozenges containing the essential oil (*46*).

Between 1889 and 1922, 17 cases of fatal poisoning due to ingestion of the essential oil were reported (*36*). A dose of as little as 3.5 ml was fatal (*47*). However, these data are old and the purity of the oil used is unknown.

Dosage forms

Essential oil in solid, semisolid or liquid preparations (*1*) and galenical preparations (*17*). Store in a well-filled, tightly closed container, protected from heat and light (*1*, *2*).

Posology

(Unless otherwise indicated)

Internal use

Daily dosage: 0.3–0.6 ml essential oil or equivalent preparations (*17*). Capsules: 1 capsule of 100–200 mg, 2–5 times daily (*48*, *49*). Lozenges: 1 lozenge of 0.2–15.0 mg dissolved slowly in the mouth, every 30–60 minutes (*32*). Mouth-

wash: 20 ml of a 0.91 mg/ml solution, gargled twice daily (*32*). Inhalation: 12 drops/150 ml boiling water (*49*).

External use

Daily dosage: several drops (*17*) or 30 ml essential oil in 500 ml lukewarm water (*35*) rubbed into the skin for local application; 5–20% essential oil in liquid and semisolid preparations; 5–10% in hydroalcoholic preparations.

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Folium Eucalypti

Definition

Folium Eucalypti consists of the dried leaves of *Eucalyptus globulus* Labill (Myrtaceae) (*1–3*).

Synonyms

Eucalyptus cordata Miq., *E. diversifolia* Miq., *E. gigantea* Dehnh., *E. glauca* D.C., *E. globulus* St Lag., *E. pulverulenta* Link (*4*).

Selected vernacular names

Alcanfor, arbre à la fièvre, Australian fever tree, bach dan xanh, Blaugummibaum, bluegum tree, calibtus, calipso, daun ekaliptus, eucalipus, eucalypto, eucalyptus, Eucalyptusblätter, feuilles d'eucalyptus, fevertree, Fieberbaum, Fieberhilbaum, gigante, gommier bleu, gommier bleu de Tasmania, gum tree, iron bark tree, kalatus, kaphur, khuynh diep, mtiulaya, nkwu-ishi, oykaliptus, Tasmanian bluegum, yukari (*1, 4–8*).

Geographical distribution

Indigenous to Australia, cultivated in subtropical regions of the world including Africa, South America (e.g. Argentina, Brazil and Paraguay), Asia (e.g. China, India and Indonesia), southern Europe and the United States of America (*1, 4, 6, 8–10*).

Description

A large tree with smooth bark, very pale or ash-grey, up to 3–20 m high. Branchlets quadrangular, glaucous. Leaves of young trees and first leaves of young shoots opposite, sessile, oval-oblong, with a cordate base, farinaceous-glaucous; older leaves dangling, spirally arranged, lanceolate-falcate, up to 30 cm long. Flowers with very short pedicels, mostly umbellate, sometimes 2–3 in a fascicle. Calyx tube double: outer tube drops early, smooth; inner tube semipersistent and warty. Stamens about 1.5 cm long. Fruit turbinate, angular, 2.0–2.5 cm in diameter (*11, 12*).

Plant material of interest: dried leaves

General appearance

Leaf lanceolate-falcate, bifacial, 8–30 cm long, 2–7 cm wide; petiole twisted, strongly wrinkled, 2–3 cm, occasionally 5 cm, in length; apex, when present, acute or acuminate; base unequal, obtuse or somewhat rounded, margin uneven, revolute; ventral and dorsal surfaces greyish-green to pale yellowish-green, coriaceous, glaucous, glabrous, glandular-punctate, with numerous small, rounded, brown dots of cork; venation pinnate-reticulate, veins of the first order running to a short distance from margin where they are anastomosed and form a vein nearly parallel with the margin (*1–3*, *8*).

Organoleptic properties

Odour: aromatic, camphoric; taste: aromatic, pungent, bitter (*1*, *3*, *8*).

Microscopic characteristics

Upper and lower epidermis composed of clear, polygonal cells with thick cutinized outer walls; both layers possess sunken stomata. Chlorenchyma differentiated into 2 palisade regions: both regions composed of 3–4 (usually 4) rows of cells which face each epidermis; in each region large, subglobular internal glands occur, lined with secretory epithelium and containing yellow oil. Parenchyma spongy, a narrow zone of loosely arranged cells between the 2 palisade regions; its cells contain rosette aggregates or monoclinic prisms of calcium oxalate crystals. Fibrovascular bundles throughout the spongy parenchyma; in midrib and petiole, interrupted arc of slightly lignified pericyclic fibres occurs just outside these bundles (*8*).

Powdered plant material

Greyish-green; fragments of chlorenchyma with numerous embedded, broken, yellow, schizogenous oil glands; calcium oxalate crystals in rosette aggregates or monoclinic prisms; fragments of epidermis with polygonal cells having very thick cuticle, numerous anomocytic stomata of more than 80 µm in diameter, fragments of sclerenchyma fibres; fragments of cork, tracheids, vessels and fibres (*1*, *3*, *8*).

General identity tests

Macroscopic and microscopic examinations, microchemical analysis and thin-layer chromatography for 1,8-cineole (*1–3*, *8*, *13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 1% fruits, and not more than 2% stems and other foreign matter (*1*–*3*).

Total ash

Not more than 6% (*2*, *3*).

Acid-insoluble ash

Not more than 0.2% (*8*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

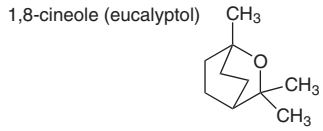
Chemical assays

Contains not less than 2% (v/w) essential oil, consisting of not less than 70% (w/w) 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1*, *3*). A thin-layer chromatography method is available for qualitative determination, using 1,8-cineole as a reference standard (*3*).

Major chemical constituents

Dried leaves contain 1–3% (v/w) essential oil (fresh leaves contain 0.4–1.6%), the major constituent of which is 1,8-cineole (54–95%). In addition, there are moderate amounts of other monoterpenes, including α-pinene (2.6%),

p-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol. Gas chromatography and gas chromatography–mass spectroscopy of the oil indicated the presence of more than 70 components, 48 of which were identified. The concentration of α-terpeneol was estimated to be 28% (*17*). The leaves are rich in tannins and ellagitannins, and also contain 2–4% triterpenes (ursolic acid derivatives), a series of phloroglucinol-sesquiterpene-coupled derivatives (macrocarpals B, C, D, E, H, I and J) and flavonoids (rutin, quercetin, quercitrin and hyperoside) (*5*, *7*, *10*, *12*, *17–19*). The structure of the major monoterpene, 1,8-cineole, is presented below.



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As an expectorant for symptomatic treatment of mild inflammation of the respiratory tract and bronchitis (*20*). Also for symptomatic treatment of asthma, fever and inflammation of the throat (*1*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), laryngitis, leukorrhoea, malaria, pimples, ringworm, wounds, ulcers of the skin, urethritis and vaginitis (*5*).

Pharmacology

Experimental pharmacology

Antibacterial and antifungal activity

An ethanol–water extract of Folium Eucalypti inhibited the growth in vitro of *Staphylococcus aureus* at a concentration of 25 µg/ml (*21*). An aqueous leaf extract inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC 0.07–1.30 mg/ml) (*22*). A methanol extract of the leaves inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (MIC 1.25–10.00 mg/ml) (*23*). A

fluidextract of the leaves inhibited the growth in vitro of *Mycobacterium tuberculosis* (MIC 6.25 mg/ml) (*24*). A methanol–water extract of the leaves inhibited the growth in vitro of *Candida albicans* (*25*).

Antiviral activity

An aqueous leaf extract inhibited the replication of influenza virus A_2 (Mannheim 57), vaccinia virus and herpes simplex virus type 2 in vitro at a concentration of 0.1% (*26*).

Antimalarial activity

Intragastric administration of a hexane leaf extract to mice (100 mg/kg body weight) did not inhibit the growth of *Plasmodium berghei* (*27*). Furthermore, administration of an aqueous (3.48 g/kg body weight) or chloroform (264 mg/kg body weight) leaf extract to chickens by gastric lavage did not inhibit the growth of *P. gallinaceum* (*28*). An ethanol–water extract of the leaves inhibited the growth in vitro of *P. falciparum* at a concentration of 75 µg/ml (*21*).

Antidiabetes activity

A hot aqueous extract of the leaves suppressed streptozocin-induced hyperglycaemia in mice when added to the diet (6.25%) and drinking-water (0.25%). The same extract did not stimulate insulin production by the pancreas (*29*). However, intragastric administration of aqueous or ethanol extracts of the leaves at a dose of 1 g/kg body weight did not suppress alloxan-induced hyperglycaemia in mice and rabbits (*30*, *31*).

Clinical pharmacology

None.

Contraindications

Preparations of Folium Eucalypti should not be administered internally to children or patients with inflammation of the gastrointestinal tract, gall bladder disease or impaired liver function (*4*, *20*).

Warnings

Folium Eucalypti preparations should not be applied to the face, especially the nose, of infants or young children (*20*). Keep out of reach of children.

Precautions

Drug interactions

Although no published drug interactions were found, a number of animal studies indicate possible concern that the leaf essential oil may induce liver

enzymes involved in drug metabolism. Therefore, the effects of other drugs may be decreased following concomitant administration (*20*, *32*).

Carcinogenesis, mutagenesis, impairment of fertility

A tincture of the leaves was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA100 and TA98 (*33*).

Pregnancy: teratogenic effects

The leaf essential oil was not teratogenic when administered subcutaneously to pregnant mice (135 mg/kg body weight) daily on days 6–15 of gestation (*34*).

Pregnancy: non-teratogenic effects

Eucalyptol (500 mg/kg body weight, administered subcutaneously) has been reported to penetrate the placenta in rodents, and reach concentrations in the fetal blood which are sufficient to stimulate hepatic enzyme activity (*35*). Therefore, Folium Eucalypti should not be administered during pregnancy without medical supervision.

Paediatric use

See Contraindications and Warnings.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions or nursing mothers. Therefore, Folium Eucalypti should not be used during lactation without medical supervision.

Adverse reactions

Excessive ingestion of Folium Eucalypti can cause nausea, vomiting and diarrhoea (*20*). Several cases of urticaria, contact dermatitis and skin irritation have been reported after therapeutic doses (*36*).

Dosage forms

Crude drug (*1*, *20*). Store in a tightly closed container, protected from light (*3*).

Posology

(Unless otherwise indicated)

Daily dosage: 4–6 g crude drug or equivalent preparations. Infusion: pour 150 ml of hot water over a half teaspoon of the leaves, allow them to stand for 10 minutes, then remove the leaves with a strainer (*10*, *20*). One cup (240 ml) of the freshly prepared infusion is drunk slowly three times daily. The vapour of the hot infusion is inhaled deeply (*10*).

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Cortex Frangulae

Definition

Cortex Frangulae consists of the dried bark of the stem and branches of *Rhamnus frangula* L. (Rhamnaceae) (*1–3*).

Synonyms

Frangula alnus Mill., *F. frangula* (L.) Karst., *F. vulgaris* Borgh., *Rhamnus alnus* Mill., *R. korolkowii* Hort. Rehd., *R. nemoralis* Salisb., *R. pentapetala* Gilib. Ortega (*1, 2, 4*).

Selected vernacular names

Alder buck, alder buckthorn, alder dogwood, alno nero, alqueshra almoqadassa, amieiro preto, Amselbaum, arrow-wood, awsag aswad, bird cherry, black alder, black alder bark, black dog wood, bois à poudre, bois noir, bourdaine, Brechwegdorn, buckthorn, buckthorn bark, casca de amiero, corteccia di frangola, cortex frangulae, Cortex rhamni frangulae, corteza de arraclau, corteza de frangula, dog wood, écorce d'aune noir, écorce de bourdaine, écorce de frangule, Faulbaum, frangola, frangula, Gelbholzrinde, Glatter Wegdorn, glossy buckthorn, Grindholz, krusinnik, kulit frangula, kutyabengekéreg, Pulverholz, Pulverholzrinde, purging buckthorn, quishrul awsagel aswad, rhamnusbast, Schwarzholz, seyah-tusseh, shagrat hhabb esh shung, siâh-touseh, Spillbaum, sporkenhoutbast, vuilboombast, Zapfenholz, Zweckenholz (*1, 4–7*).

Geographical distribution

Indigenous to Mediterranean countries and temperate regions of Africa, western Asia and Europe (*1, 8*).

Description

A shrub, 3–5 m high with non-thorny stalks and dark-red to purplish-blue young branches spotted with greenish lenticels. Leaves alternate and ovate, entire or slightly sinuate along the margin, and have parallel secondary veins which curve as they meet the edge of the blade. Flowers small, greenish-white, hermaphrodite, pentamerous, arranged in axillary clusters of

2–3. Fruit a drupe, red at first, then black at maturity, with 2 or 3 seeds (*1*, *9*, *10*).

Plant material of interest: dried bark

The fresh bark contains free anthrones and must be stored for at least 1 year or artificially aged by heat or aeration before therapeutic use (*1*, *11*, *12*).

General appearance

Single or double quills, rarely in channelled pieces; usually 15 cm long, 0.5–2 cm wide and extremely thin (not more than 2 mm thick). Outer surface greyish-brown or purplish-black, wrinkled, with numerous transversely elongated whitish lenticels; sometimes bearing patches of foliaceous lichen, with small black apothecia; when gently scratched, crimson colour of inner layers of cork becomes evident. Inner surface reddish-yellow to dark brown; fine longitudinal striations, becoming red when moistened with dilute solutions of alkali (Bornträger's test). Fracture, short in the outer part and slightly fibrous in the inner part (*1*, *2*).

Organoleptic properties

Odour: characteristic; taste: sweetish then slightly bitter and astringent; mucilaginous (*1*, *8*).

Microscopic characteristics

Cortex yellowish-brown, consisting of thin-walled parenchyma, containing scattered cluster crystals of calcium oxalate and few small starch grains, and showing large cells filled with mucilage and few groups of slightly lignified fibres, each up to 40 µm wide. Phloem yellowish-brown, traversed by numerous, somewhat wavy medullary rays, 1–3 cells wide and 10–25 cells high, and showing numerous tangential groups of strongly lignified bast fibres, accompanied by prismatic crystals of calcium oxalate, forming a crystal sheath around each group; individual fibres 12–24 µm in diameter (*1*).

Powdered plant material

Yellowish-brown. Fragments of reddish-brown cork; fragments of groups of lignified bast fibres, accompanied by a calcium oxalate crystal sheath; occasional fragments of slightly lignified fibres; fragments showing cells of medullary rays, with yellow contents which turn red with solutions of alkali or with sodium hypochlorite solution; cluster crystals of calcium oxalate, 10–25 µm in diameter; prismatic crystals of calcium oxalate, 7–15 µm long; few starch grains 3–10 µm in diameter; sclereid cells absent (*1*, *2*).

General identity tests

Macroscopic, microscopic and microchemical (Bornträger's test) examinations and thin-layer chromatography for characteristic hydroxyanthracene glycosides (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign matter

Not more than 1% (*2*).

Total ash

Not more than 6% (*2*).

Acid-insoluble ash

Not more than 2% (*1*).

Loss on drying

Not more than 10% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

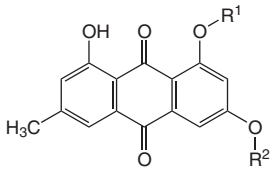
Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

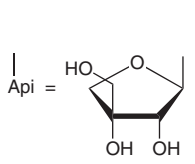
Contains not less than 7.0% of glucofrangulins, calculated as glucofrangulin A, determined by spectrophotometry at 515 nm (*2*). The high-performance liquid chromatography method reported for quantitative analysis of cascarosides (*16*) can also be considered.

Major chemical constituents

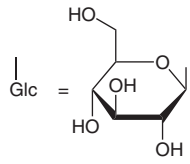
The active constituents are hydroxyanthraquinone glycosides (3–8%) consisting of monoglycosides and diglycosides of frangula emodin, with the diglycosides, glucofrangulins A and B, being the major compounds. The major monoglucosides are frangulins A and B (*17*). Other anthranoid derivatives present include emodin anthrone-6-*O*-rhamnoside (franguloside), as well as physcion and chrysophanol in glycosidic and aglycone forms (*17*, *18*). In the fresh bark, anthraquinones are not present, but exist as their reduced anthrone and dianthrone glycosides, which are converted by oxidation during drying and storage, or by accelerated heat and air treatment (*4*, *6*, *8*, *9*, *17*). The structures of the major anthraquinone glycosides, free anthraquinones and frangula emodin anthrone are presented below.



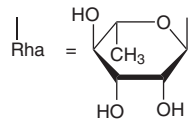
	R^1	R^2
frangula emodin	H	H
frangulin A	H	Rha
glucofrangulin A	Glc	Rha
frangulin B	H	Api
glucofrangulin B	Glc	Api



D-*apio*-β-D-furanosyl



β-D-glucopyranosyl



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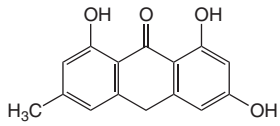

frangula emodin anthrone

Medicinal uses

Uses supported by clinical data

Short-term treatment of occasional constipation (*1*, *9–11*). As a single dose, for total intestinal evacuation before X-rays and other diagnostic examinations when electrolyte solutions alone are insufficient for adequate evacuation or the use of electrolyte solutions is not possible (*11*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a cathartic (*1*).

Uses described in folk medicine, not supported by experimental or clinical data

Internally for treatment of diabetes and externally for skin irritations (*6*).

Experimental pharmacology

Laxative effects

The pharmacological effects of Cortex Frangulae are associated with the hydroxyanthraquinone glycosides, glucofrangulins A and B, and frangulins A and B (*17*). After oral administration of Cortex Frangulae, the hydroxyanthracene glycosides are not absorbed in the upper intestine, but are hydrolysed in the colon by intestinal bacteria to form the pharmacologically active metabolites. These metabolites are partially absorbed in the colon and act as a stimulant and irritant to the gastrointestinal tract, as does senna (*11*, *18*, *19*, *20*). The mechanism of action, similar to that of senna, is twofold. Firstly, there is stimulation of colonic motility, resulting in augmented propulsion, and accelerated colonic transit (which reduces fluid absorption from the faecal mass). Secondly, there is an increase in paracellular permeability across the colonic mucosa, probably due to inhibition of sodium/potassium-transporting adenosine triphosphatase or inhibition of chloride channels (*18*, *21*). The increased permeability results in increased water content in the colon (*11*, *21*).

The laxative effect of Cortex Frangulae is not generally observed until 6–8 hours after oral administration. Hydroxyanthracene glycosides are excreted predominantly in the faeces but are also excreted to some extent in urine, producing an orange colour; anthrones and anthranols will also pass into breast milk (*18*).

Toxicity and overdose

As with other anthraquinone laxatives, the major symptoms of overdose are gripes and severe diarrhoea with consequent loss of fluid and electrolytes (*22*). Treatment of overdose should be supportive with generous amounts of fluid. Electrolyte levels should be monitored, particularly those of potassium. This is especially important in children and the elderly (*22*).

Clinical pharmacology

None.

Contraindications

Cortex Frangulae should not be administered to patients with intestinal obstruction and stenosis, atony, inflammatory diseases of the colon (such as ulcerative colitis, irritable bowel syndrome, Crohn disease), appendicitis, severe dehydration with water and electrolyte depletion, or chronic constipation (*9*, *19*, *23*). As with other stimulant laxatives, Cortex Frangulae is contraindicated in patients with cramps, colic, haemorrhoids, nephritis, or any undiagnosed abdominal symptoms such as abdominal pain, nausea or vomiting (*22*). Cortex Frangulae and other anthranoid laxatives are contraindicated during pregnancy because of their pronounced action on the large intestine and the lack of data on their toxicology (*24*, *25*). As anthranoid metabolites may appear in breast milk, Cortex Frangulae should not be used during lactation, since there are insufficient data to assess the potential for pharmacological effects in the breastfed infant (*25*). Use of Cortex Frangulae for children under the age of 12 years is contraindicated (*11*).

Warnings

Cortex Frangulae should only be used if no effect can be obtained through a change of diet or by the use of bulk-forming laxatives. Patients should also be warned that certain constituents of the bark are excreted by the kidney and may colour the urine orange, which is harmless. Cortex Frangulae and other stimulant laxatives should not be used by patients with abdominal pain, nausea or vomiting. The use of stimulant laxatives for longer than 2 weeks requires medical supervision. Rectal bleeding or failure to have a bowel movement after taking a laxative may indicate a serious condition. Chronic use may result in aggravation of constipation with laxative dependence and need for increased dosages, and disturbances of water and electrolyte balance (e.g. hypokalaemia). Chronic use may also lead to colonic dysfunction (atonicity) and melanotic pigmentation of the colonic mucosa (pseudomelanosis coli), which is harmless (*22*). Laxative abuse resulting in diarrhoea and consequent fluid and electrolyte losses (mainly of potassium) may cause albuminuria, haematuria, and cardiac and neuromuscular dysfunction. Neuromuscular dysfunction may arise particularly in the case of concomitant use of cardiotonic glycosides (e.g. digoxin, digitalis and strophanthin), diuretics, corticosteroids or liquorice root (*22*).

Precautions

General

Cortex Frangulae and other laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, because of the possibility of electrolyte imbalance (*22*).

Drug interactions

Increased intestinal transit time may result in reduced absorption of orally administered drugs (*26*). Electrolyte imbalances, such as hypokalaemia, may potentiate the effects of cardiotonic glycosides (e.g. digoxin, digitalis and strophanthus). Hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs (e.g. quinidine) that change sinus rhythm by affecting potassium channels. Hypokalaemia caused by drugs such as thiazide diuretics, adrenocorticosteroids or liquorice root may be exacerbated, and imbalance of other electrolytes may be aggravated (*11*).

Drug and laboratory test interactions

Anthranoid metabolites may not be detectable in faeces or urine by standard methods. Thus faecal excretion measurements may not be reliable (*26*). Urinary excretion of certain anthranoid metabolites may cause discoloration of the urine which is not clinically relevant, but may cause false positives in urinary urobilinogen tests and in estrogen measurements using the Kober procedure (*27*).

Carcinogenesis, mutagenesis, impairment of fertility

Although chronic use of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer, no causal relationship has been demonstrated (*28–31*).

Various Cortex Frangulae extracts have been shown to be genotoxic in several in vitro systems, resulting in bacterial mutation, and chromosomal aberration and DNA-repair defects in mammalian cells. However, no mutagenicity was observed in a gene mutation assay in mammalian cells (*23*). Frangula emodin was mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strain TA1537 only, but gave inconsistent results in gene mutation assays in mammalian cells. Frangula emodin was also a strong inducer of unscheduled DNA synthesis in primary rat hepatocytes, but gave negative results in the sister chromatid exchange assay (*18*, *23*, *32*, *33*).

Pregnancy: teratogenic effects

The teratogenic effects of Cortex Frangulae have not been evaluated. (See also Contraindications.)

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Adverse reactions

Single doses of Cortex Frangulae may result in cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage (*11*). Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools.

Long-term laxative abuse may lead to electrolyte imbalance (hypokalaemia and hypocalcaemia being the most important), metabolic acidosis, malabsorption of nutrients, weight loss, albuminuria and haematuria (*34*, *35*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Secondary aldosteronism may occur due to renal tubular damage after prolonged use. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported in laxative abuse (*36*). Pseudomelanosis coli has been observed in individuals taking anthraquinone laxatives for extended time periods (*22*, *35*). The pigmentation is harmless and usually reversible within 4–12 months after the drug is discontinued (*35*). Conflicting data exist on other toxic effects after long-term use such as damage to the autonomous nervous system of the colon (*35*, *37*). In incontinent patients using anthranoid laxatives, prolonged exposure of the skin to faeces may cause skin damage (*38*).

Use of the fresh bark of *Rhamnus frangula* may cause severe vomiting, with possible abdominal spasms (*18*).

Dosage forms

Finely cut and powdered crude drug, powder, dried extract, liquid and solid preparations (*8*). Store in a tightly closed, light-resistant container for a maximum of 3 years (*1*, *2*).

Posology

(Unless otherwise indicated)

The correct dosage for the treatment of occasional constipation is the smallest dosage necessary to maintain a soft stool. Daily dosage: 0.5–2.5 g crude drug taken directly or in a decoction; 0.5–2.5 ml 25% ethanol extract (*18*); all preparations standardized to contain 20–30 mg hydroxyanthracene derivatives calculated as glucofrangulin A (*11*); taken at bedtime, or in two divided doses, one in the morning and one at bedtime.

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Folium et Cortex Hamamelidis

Definition

Folium et Cortex Hamamelidis consists of the dried or fresh leaves and/or the dried bark of *Hamamelis virginiana* L. (Hamamelidaceae).

Folium Hamamelidis consists of the dried (*1*, *2*) or fresh leaves (*3*), and Cortex Hamamelidis consists of the dried bark of the trunk and twigs of *Hamamelis virginiana* L. (*2*, *4*).

Synonyms

Hamamelis androgyna Walt., *H. caroliniana* Walt., *H. corylifolia* Moench., *H. dentata* Moench., *H. dioica* Walt., *H. estivalis* Raf., *H. macrophylla* Pursh., *H. nigra* Raf., *H. parvifolia* Raf., *H. rotundifolia* Raf., *H. virginata* sic, *H. virginiae* L., *H. virginiana* ssp. *parvifolia* Nutt., *H. virginica* L., *Trilopus dentata* Raf., *T. estivalis* Raf., *T. nigra* Raf., *T. parvifolia* Raf., *T. rotundifolia* Raf., *T. virginica* Raf. (*5*, *6*).

Selected vernacular names

Amamelide, Amerikamansaku, cortice de hamamelis, feuilles d'hamamélis, feuilles du noisetier de la sorcière, folhas de hamamelis, hamamelis, hamamélis de virginie, Hexenhasel, magician's rod, noisetier de sorcière, oczar, pistachio nut, snapping hazelnut, spotted alders, striped alder, tobacco wood, varázsdió levél és kéreg, vilin virginsky, virginische Zaubernuss, virginischer Zauberstrauch, white hazel, winter bloom, witch hazel, Zauberhasel, Zaubernuss (*5–8*).

Geographical distribution

Indigenous to the Atlantic coast of North America, found in damp woods ranging from Nova Scotia to Florida and as far west as Texas (*6*, *8*, *9*).

Description

A tall shrub or small tree, up to 4.6 m high. Branches highly branched. Leaves alternate, stipulate, short-petioled, unequilaterally ovate or rhomboid-ovate, with oblique base and sinuate or sinuate-dentate margin. Flowers thread-like, golden-yellow; appear in axillary clusters as leaves fall in autumn and at about the same time as fruits ripen from blossoms of the previous year. Fruit a

2-beaked, 2-celled, woody capsule dehiscing loculicidally from the top, each cell containing a single black seed (*8*, *10*, *11*).

Plant material of interest: dried and fresh leaves, dried bark

General appearance

Folium

Green or greenish-brown, often broken, crumpled and compressed into more or less compact masses. Lamina 5–12 cm long, 3–8 cm wide, broadly ovate to obovate; base oblique and asymmetric; apex acute or, rarely, obtuse; margins of lamina roughly crenate or dentate. Venation pinnate and prominent on the abaxial surface; usually 4–6 pairs of secondary veins attached to main vein, leaving at an acute angle and curving gently to marginal points where there are fine veins often at right angles to secondary veins (*1*).

Cortex

Channelled, seldom quilled or in strips, up to 3 cm wide and 2 mm thick. Outer surface light yellowish-brown or reddish-brown, has thin, whitish or greyish-brown cork with numerous lenticels; inner surface yellowish-brown to reddish-brown, longitudinally striated. Fracture splintery and fibrous (*9*).

Organoleptic properties

Folium

Odour: slight; taste: astringent, slightly aromatic, bitter (*8*).

Cortex

Odourless; taste: strongly astringent, slightly bitter (*2*, *9*).

Microscopic characteristics

Folium

Upper epidermis of leaf composed of slightly elongated cells with straight to slightly sinuous walls; walls moderately and sometimes unevenly thickened; no stomata; underlying palisade cells fairly small and distinct. Lower epidermis composed of polygonal cells with very sinuous outline; walls thinner and more uniform than those of upper epidermis; paracytic stomata fairly numerous but rather faint and indistinct; underlying cells of spongy mesophyll frequently brown, appear as clearly defined honeycomb network. Covering trichomes characteristic, stellate, found fragmented, occasionally entire, composed of 4–12 elongated, conical cells united at their bases to form a radiating structure; each cell has moderately and slightly unevenly thickened wall which is slightly lignified. Linear idioblasts, composed of lignified cells, found scattered across

entire thickness of lamina. Prismatic calcium oxalate crystals scattered, occasionally found in clusters, as well as forming a sheath (*12*).

Cortex

Sclereids abundant, vary considerably in size, are of 2 types: rounded to oval, or subrectangular; heavily thickened, usually in groups of just 2 or 3 cells, but smaller cells often form larger groups; walls have numerous, conspicuous branched pits and striations, particularly in the larger cells; other type of sclereids more regular in size and form, frequently found associated with the cork, occurring as a layer of small, polygonal cells with no intercellular spaces. Fibres occur in groups surrounded by a sheath of prismatic calcium oxalate crystals; individual fibres very thick-walled and lignified with indistinct lumen with calcium oxalate prismatic crystals scattered as well as in the parenchyma surrounding the fibres. Crystals also occasionally found associated with thicker-walled sclereids; crystals fairly uniform in size, although a few very large prisms may occur. Parenchyma cells thin-walled, several filled with dark brown contents. Medullary rays uniseriate, composed of rounded cells with slightly thickened walls. Cork cells thin-walled and polygonal. Fragments of lignified xylem tissue from adherent wood infrequent and consist of narrow tracheids with conspicuous bordered pits, accompanied by thin-walled fibres and pitted medullary ray cells. Starch grains rare; a few small, spherical grains may be found in some parenchymatous cells (*12*).

Powdered plant material

Folium

Brownish-green; fragments of adaxial epidermis with wavy anticlinal walls; abaxial epidermis with stomata, some paracytic, others atypical; covering trichomes, stellate, either entire or broken, composed of 4–12 cells united at their bases; cells elongated and conical, usually up to 250 µm long, thick-walled with clearly visible lumen with often brown contents. Fibres lignified and thick-walled, isolated or in groups; accompanied by sheath of prismatic calcium oxalate crystals. Parenchymatous palisade cells small and cylindrical; irregular-shaped cells of spongy mesophyll; sclereids, frequently enlarged at one or both ends, 150–180 µm long, whole or fragmented; fragments of annular or spiral vessels; isolated prismatic calcium oxalate crystals (*1*).

Cortex

Masses of brownish or yellowish cork cells, some lignified; groups of parenchyma cells with tannin or small starch grains; strands of lignified bast; tracheae with bordered pores; strongly lignified wood fibres with slit-like or bordered pores; crystal fibres containing monoclinic prismatic calcium oxalate crystals (up to 40 µm in length) (*13*).

General identity tests

Macroscopic and microscopic examinations (*1*), thin-layer chromatography (*1*, *2*) and high-performance liquid chromatography (*5*) for characteristic tannin constituents.

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Folium

Not more than 7% stems, and not more than 2% other foreign matter (*1*).

Cortex

Not more than 2% foreign matter (*2*, *4*).

Total ash

Folium

Not more than 7% (*1*).

Cortex

Not more than 6% (*2*).

Acid-insoluble ash

Folium

Not more than 2% (*1*).

Cortex

Not more than 1.5% (*2*).

Alcohol-soluble extractive

Folium

To be established in accordance with national requirements.

Cortex

Not less than 20% using 45% alcohol (*2*).

Loss on drying

Folium

Not more than 10% (*1*).

Cortex

Not more than 12% (*4*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Folium and Cortex

Chemical, sulfated ash and water-soluble extractive tests to be established in accordance with national requirements.

Folium

Alcohol-soluble extractive test to be established in accordance with national requirements.

Chemical assays

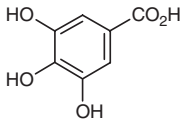
Folium: contains not less than 3% tannins (*1*). Cortex: contains not less than 4% tannins (*4*). Thin-layer chromatography is used for qualitative and quantitative analysis of tannins (*1*). A high-performance liquid chromatography method for quantitative analysis of condensed and hydrolysable tannins has been developed (*17*, *18*).

Major chemical constituents

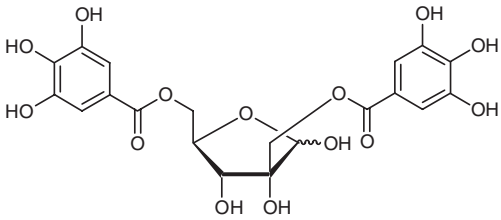
The major constituents of the dried leaf and bark are tannins (up to 10%). Both hydrolysable and condensed tannins are present, with the latter predominating (*9*, *11*, *19*). Folium tannins are a mixture of gallic acid (10%), hydrolysable

hamamelitannin (1.5%) and condensed proanthocyanidins (88.5%) (*17*). Cortex tannins are similar qualitatively, but have a much higher hamamelitannin level (up to 65% of a hydroalcoholic extract) (*11*).

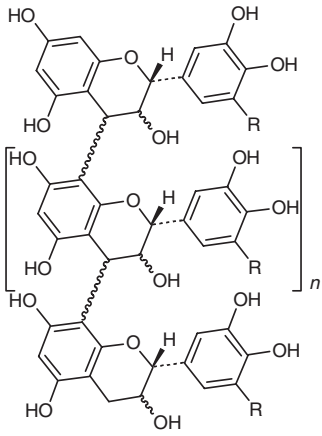
The structures of gallic acid, hamamelitannin and condensed proanthocyanidins are presented below.



gallic acid



hamamelitannin



proanthocyanidins
procyanidin $n = 0$, R = H
prodelphinidin $n = 0$, R = OH

Medicinal uses

Uses supported by clinical data

Topically for minor skin lesions, bruises and sprains (*3*, *5*, *20*), local inflammation of the skin and mucous membranes (*3*, *5*, *20–24*), haemorrhoids (*3*, *5*, *20*, *25–28*) and varicose veins (*3*).

Uses described in pharmacopoeias and in traditional systems of medicine

Topically as a haemostat (*27*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of colitis, diarrhoea, dysentery, dysmenorrhoea, eye inflammations, haematuria, kidney pains, neuralgia, nosebleeds and excessive menstruation. Also as a tonic (*6*, *7*, *19*).

Pharmacology

Experimental pharmacology

Astringent activity

The phenolic constituents of Folium et Cortex Hamamelidis, particularly the tannins (e.g. hamamelitannin), aldehydes and oligomeric proanthocyanidins, are responsible for its astringent activity (*6*, *18*, *29*, *30*). Similar to other astringent drugs, application of Hamamelidis[1] preparations to the skin and mucosa in low concentrations sealed cell membranes and reduced capillary permeability (*6*, *30*). Higher concentrations precipitated proteins and thickened colloidal tissue, forming a thin membrane in the wound region, and slightly compressed the skin tissue beneath it (*6*). Alcohol extracts of Hamamelidis had strong astringent action, with the bark extract being slightly superior to the leaf extract (*31*).

The healing effect of Hamamelidis distillate was compared with hydrogen peroxide on skin damaged by application of dichlorodiethyl sulfide (mustard gas) in various animal models. The distillate was more effective than hydrogen peroxide in reducing the occurrence of pus in the affected skin areas. Furthermore, subsequent treatment of the purulent skin areas with a 20% Hamamelidis ointment reduced the incidence of suppuration as compared with hydrogen peroxide treatment (*6*, *32*).

Venotonic activity

The venotonic effects of leaf preparations (steam distillate, tincture or alcohol extract) were tested by measuring the blood supply to the rear paw of rabbits (*33*). A decrease in blood supply was observed after intra-arterial administration of the distillate. This effect was not influenced by concomitant administration of adrenergic, adrenolytic or myotonic drugs (*33–35*).

Antibacterial activity

An aqueous extract of the leaves inhibited the growth in vitro of *Escherichia coli* (MIC 0.4 mg/ml), *Staphylococcus aureus* (MIC 0.4 mg/ml), *Bacillus subtilis* (MIC 1.1 mg/ml) and *Enterococcus faecalis* (MIC 3.0 mg/ml). Aqueous extracts of the bark inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC for all 10.0 mg/ml) (*36*).

Antioxidant activity

Hamamelitannin inhibited the production of superoxide anion radicals (IC_{50} 1.38 µmol/l) and hydroxyl radicals (IC_{50} 5.46 µmol/l), as measured by electron spin resonance spectrometry (*37*, *38*). Hamamelitannin also suppressed the depolymerization of hyaluronic acid and protected human dermal fibroblasts against damage induced by superoxide anion radicals (at concentrations of

[1] Refers to Folium et Cortex Hamamelidis.

1 mmol/l and 10 mmol/l, respectively) (*37*). Hamamelitannin and gallic acid protected murine dermal fibroblasts against damage induced by superoxide anion radicals (IC_{50} 1.31 µmol/l and 1.01 µmol/l, respectively) (*38*). Both tannins had free radical scavenging activity. For superoxide anion scavenging, the IC_{50} was 1.31 µmol/l for hamamelitannin and 1.01 µmol/l for gallic acid, compared with 23.31 µmol/l for ascorbic acid. For hydroxyl radical scavenging, the IC_{50} was 5.46 µmol/l for hamamelitannin and 78.04 µmol/l for gallic acid. For singlet oxygen scavenging, the IC_{50} was 45.51 µmol/l for hamamelitannin and 69.81 µmol/l for gallic acid (*39*).

Anti-inflammatory activity

Hamamelidis extracts and isolated chemical constituents have anti-inflammatory activity both in vitro and in vivo. Intraperitoneal administration of a 70% ethanol extract of the leaves (200 mg/kg body weight) significantly inhibited the chronic phase of carrageenan-induced rat footpad oedema (*40*). Hamamelitannin and galloylated proanthocyanidins isolated from Hamamelidis are potent inhibitors of 5-lipoxygenase (IC_{50} range 1.0–18.7 µg/ml). Topical application of a hydroalcoholic extract of the bark (250 µg/ml) inhibited croton oil-induced ear oedema in mice. In addition to anti-inflammatory activity, this study demonstrated that the proanthocyanidin fraction of the hydroalcoholic extract was active against herpes simplex virus type 1 (ED_{50} 11 µg/ml), and also inhibited α-glucosidase (ED_{50} 0.35 µg/ml) and human leukocyte elastase (ED_{50} 1.4 µg/ml) (*41*).

Clinical pharmacology

Anorectal complaints

The astringent properties of Hamamelidis extracts have led to their use in ointments and suppositories for the treatment of anorectal complaints, such as haemorrhoids (*25–27*). In a clinical study without controls of 75 patients with acute stage 1 haemorrhoidal symptoms, the efficacy of rectal ointments containing either a Hamamelidis fluidextract or bismuth subgallate was assessed. After application of either ointment twice daily for 3 days, significant improvement was observed in pruritus, burning sensation and pain ($P < 0.001$). Marked recovery was noted after 3 weeks of therapy (*25*). A randomized, double-blind trial compared the efficacy of rectal ointments containing either a Hamamelidis fluidextract, bismuth subgallate or a local anaesthetic in the treatment of 90 patients with acute stage 1 haemorrhoidal symptoms. The local anaesthetic was present in two control ointments which also contained either policresulen or fluocinolone acetonide. After 21 days of treatment, all four ointments were equally effective in improving pruritus, bleeding, burning sensation and pain (*26*).

The efficacy of a Hamamelidis ointment containing 25 g aqueous distillate/100 g ointment base (equivalent to about 4 g drug) was compared to a Hamamelidis reference preparation in a study without controls of 70 patients

with various anorectal complaints. Preparations were applied to the affected skin or transitional mucosa three times daily either alone or in combination with sclerotherapy. After 4 weeks of treatment, symptoms such as pruritus, burning sensation and pain were eliminated in 60% of the patients treated with the Hamamelidis ointment (*28*).

Anti-inflammatory activity

The anti-inflammatory efficacy of an aftersun lotion containing 10% Aqua Hamamelidis was compared with that of two Hamamelidis-free aftersun lotions in 30 healthy volunteers. Each volunteer received four doses of ultraviolet B in a modified ultraviolet B erythema test. Chromametry and visual scoring were used to determine the degree of erythema at 7, 24 and 48 hours after irradiation. The lotion containing Hamamelidis suppressed erythema by 20% at 7 hours and by 27% at 48 hours, whereas the degree of suppression seen with the Hamamelidis-free lotions was 11% and 15%, respectively (*42*).

A randomized, double-blind study of 48 patients assessed the anti-inflammatory efficacy of topical application of a Hamamelidis distillate in a phospholipid-containing vehicle, hydrocortisone, camomile and four drug-free vehicle-based preparations. Erythema induced by ultraviolet light or repeated stripping of the skin with adhesive tape was suppressed only by the Hamamelidis preparation (0.64 mg or 2.5 mg Hamamelidis ketone per 100 g vehicle) and hydrocortisone cream (1%). However, the hydrocortisone cream was superior to all other preparations tested (*21*).

Vasoconstriction

A randomized, placebo-controlled study assessed the vasoconstrictive effects of an aqueous propylene glycol extract of Hamamelidis in 30 healthy volunteers. The extract produced a reduction in skin temperature as compared with the placebo (*6*, *43*). The anti-inflammatory effects of a Hamamelidis ointment containing 25 g aqueous distillate/100 g ointment base (about 4 g drug) were analysed in five patients with dermatoses and 22 healthy volunteers. Fluvography measurements indicated that in both groups the ointment reduced the thermal conductivity of the skin due to vasoconstriction, suggesting a mild anti-inflammatory activity. These data were confirmed by transcutaneous oxygen measurements (*44*).

Eczema

A randomized, double-blind, placebo-controlled trial compared the efficacy of three creams containing either a Hamamelidis distillate, 0.5% hydrocortisone or a drug-free vehicle in the symptomatic treatment of 72 patients with moderately severe atopic eczema. All treatments reduced the incidence of itching, scaling and erythema after 1 week of treatment: the cream containing Hamamelidis distillate was no more effective than that containing the placebo (*45*).

The efficacy of two Hamamelidis ointments (differing only in the ointment base), containing 25 g aqueous distillate/100 g ointment base (equivalent to about 4 g drug), for the treatment of endogenous eczema (neurodermatitis) and toxic degenerative eczema (attrition eczema) was compared in a placebo-controlled, double-blind study (the placebo was not described). Symptomatic improvements in itching, redness, burning sensation and desquamation of the skin were observed in the 36 patients with endogenous eczema (neurodermatitis) with both Hamamelidis preparations after treatment for 39 days. Eighty patients with toxic degenerative eczema (attrition eczema) treated with the Hamamelidis ointments showed improvements in rough skin, redness, burning sensation and desquamation of the skin after 28 days of treatment (*23*).

A randomized, double-blind comparison study assessed the efficacy of ointments containing either a standardized extract of the dried leaves or bufexamac in the treatment of 22 patients with bilateral, moderately severe endogenous eczema (neurodermatitis). Patients were treated three times daily for an average of 17 days. Comparison of the patients' forearms showed that both treatments reduced the severity of symptoms such as desquamation of the skin, redness, itching and lichenification, with desquamation showing the highest reduction (55%). No differences were observed in the global assessment of the therapy or the severity of symptoms between treatments (*24*).

In a pilot study of 37 patients with endogenous eczema (neurodermatitis), a cream containing a Hamamelidis leaf extract was applied twice daily for 2 weeks. Following treatment, considerable improvement in symptoms such as inflammation and itching was noted in 24 patients (*46*).

Analgesic activity

In a randomized clinical trial involving 266 patients undergoing episiotomy, the efficacy of three analgesic treatments was investigated to determine their effects on pain, bruising and oedematous swelling. The treatments tested were local application of: a cream containing Hamamelidis water BPC 1973; a reference cream containing 1% hydrocortisone and a local anaesthetic; and ice packs. Oral paracetamol and salt baths were also used as needed. The efficacy of all three analgesic treatments appeared to be equal (*22*).

Antiviral activity

The efficacy and safety of an ointment prepared with a special extract from the bark was assessed in a randomized, double-blind, placebo-controlled study for the treatment of herpes labialis infection. Thirty-four patients were treated within 48 hours of recurrence of symptoms, and treatment (daily) lasted for 8 days. By the end of the therapy, the size of the inflamed area was significantly reduced in patients treated with the Cortex Hamamelidis ointment as compared with placebo treatment ($P = 0.022$) (*47*).

Contraindications

No information available.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Aqueous extracts of the dried leaves were not carcinogenic when administered subcutaneously to rodents (10 mg/animal) (*48*).

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium et Cortex Hamamelidis should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Allergic contact dermatitis may occur in sensitive individuals (*49*, *50*).

Dosage forms

Dried leaves and bark for decoctions; steam distillate, ointment and suppositories (*3*, *9*). Fresh leaves and twigs are collected in the spring and early summer to make a steam distillate (*3*). Store in a well-closed container, protected from light (*19*).

Posology

(Unless otherwise indicated)
External use: steam distillate, undiluted or diluted 1 : 3 with water to make poultices; 20–30% in semisolid preparations (*3*). Extracts: in semisolid and liquid preparations corresponding to 5–10% of the crude drug (*3*, *5*). Crude drug: decoctions from 5–10 g to 1 cup (250 ml) water for poultices and wound irrigation (*3*, *5*). Rectal suppositories: 1–3 times daily the quantity of a preparation corresponding to 0.1–1.0 g crude drug, use Hamamelidis water undiluted or diluted 1 : 3 with water (*3*, *5*). Other preparations: several times daily, corresponding to 0.1–1.0 g drug in preparations, or witch hazel water undiluted or diluted with water (*3*).

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Semen Hippocastani

Definition

Semen Hippocastani consists of the dried ripe seeds of *Aesculus hippocastanum* L. (Hippocastanaceae) (*1*, *2*).

Synonyms

Aesculus castanea Gilib., *A. procera* Salisb., *Castanea equina*, *Hippocastanum vulgare* Gaertner (*3*). Not to be confused with the common chestnut, *Castanea dentata* (Marshall) Burkh. (Fagaceae) (*4*) or related *Castanea* species (*5*).

Selected vernacular names

Abu farwat el hhussan, castagna amare, castagna cavallina, castagna di cavalle, castagno d'India, castan, castandas da India, castanheiro da India, castaño de Indias, chata, châtaignier de cheval, châtaignier de mer, common horse chestnut, conqueror tree, custul, gemeine Kastanie, gemeine Rosskastanie, hippocastani semen, horse chestnut, karu, marronier d'Inde, naru, paardekastanje, Pferdekastanie, qastanah baria, Rosskastanie, seiyo-tochinoki, seiyoutochinoki, semen castaneae equinae, shahbalout-e hendi, vadgesztenyemag, weisse Rosskastanie, wilde kastanje, wilde kest (*3*, *6*).

Geographical distribution

Indigenous to western Asia, is now widely cultivated in parks, gardens and along city streets of many countries worldwide, including those in Europe, and the United States of America (*7*).

Description

A tree, up to 30 m high and 2 m in circumference, with large sticky buds and dense, broad, usually orbicular, or occasionally pyramidal, crown. Leaves up to 20 cm long and 10 cm wide, with 15–20 cm long petioles; composed of 5–7 large sessile leaflets, median leaflet largest, outer leaflets much smaller. Blades obovate or oblong, tapering at the base, abruptly mucronate, irregularly serrate at the margin; dorsal side glabrous; ventral side with soft hairs. Flowers have 5 petals with an orbicular limb, imbricate at the margins, white, with yellow spot at base which later turns pink; arranged in erect dense panicles up to 20–

30 cm long; rachis and pedicel with reddish-brown hairs; calyx cylindrical to campanulate and pubescent; stamens hairy at the base; ovary covered with soft hairs and prickles. Capsules spiny, usually with 1 large seed (*7*).

Plant material of interest: dried ripe seeds

General appearance

Globulous or ovoid, 2–4 cm in diameter. The 2 large cotyledons fleshy, oily and starchy, often connate with a line of suture more or less visible; covered by a shiny dark-brown tegument with a large whitish spot corresponding to the hilum; tegument creamy white in the immature seed, takes on a brown tinge during maturation, becoming dark brown when mature. Curved radicle occupies a depression either on the commissure of the cotyledons or on the dorsal side of 1 of the cotyledons (*1*, *2*).

Organoleptic properties

Odour: slight; taste: bitter, acrid (*1*).

Microscopic characteristics

Seed envelope made up of polygonal cells radially oriented in a transverse section of the seed. Underneath the envelope are numerous layers of sclerenchyma cells with dense, roughly mottled, yellowish-brown thick walls; loose parenchyma, colourless, consisting of a few layers of cells, with rigid walls; sparse annulate or spiral vessels. Tissue of the cotyledons made up of cells with thin, colourless walls, full of starch and lipids. Characteristic starch grains found singly, either spherical (15–25 µm in diameter) or irregular (pear- or kidney-shaped); also numerous small (5–10 µm in diameter), spherical starch grains and a few grains clustered into groups of 2–4 (*1*, *2*).

Powdered plant material

Yellowish-grey. Characteristic starch grains found singly, either spherical (15–25 µm in diameter) or irregular (pear- or kidney-shaped); also numerous small (5–10 µm in diameter), spherical starch grains and a few grains clustered into groups of 2–4. Oil droplets of different sizes; fine fragments of colourless cell walls from the cotyledons; fragments of seed envelope brownish-yellow; and parenchyma and roughly mottled sclerenchyma cells (*1*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the characteristic triterpene saponin, aescin (also known as escin) (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO quality control methods for medicinal plants (*8*).

Foreign organic matter

Not more than 2% (*1*).

Total ash

Not more than 4% (*1*, *2*).

Loss on drying

Not more than 10% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

Other purity tests

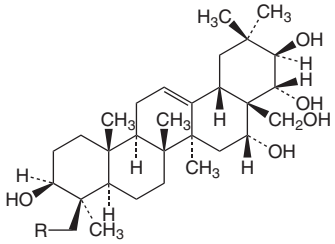
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 3.0% triterpene saponins, calculated as aescin (escin), determined by spectrophotometry at 540 nm (*1*, *2*). High-performance liquid chromatography (*11*) and thin-layer chromatography–densitometry (*11*, *12*) procedures for the quantitative analysis of triterpene saponins have also been developed.

Major chemical constituents

The major constituents are triterpene saponins (up to 10%), collectively referred to as aescin (also known as escin), and are considered the active therapeutic principles. Aescin exists in three forms, α-aescin, β-aescin and cryptoaescin, which are differentiated by their physical properties. β-aescin is a mixture of more than 30 different glycosides derived from the triterpene aglycones protoaescigenin (also known as protoescigenin) and barringtogenol C. Other constituents include flavonoids (e.g. quercetin, kaempferol and their glycosyl derivatives) (*3*, *5*, *7*). The structures of barringtogenol C and protoaescigenin are presented below.



barringtogenol C R = H

protoaescigenin R = OH

Medicinal uses

Uses supported by clinical data

Internally, for treatment of symptoms of chronic venous insufficiency, including pain, feeling of heaviness in the legs, nocturnal calf-muscle spasms, itching and oedema (*13–21*). Externally, for the symptomatic treatment of chronic venous insufficiency, sprains and bruises (*22–24*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of coronary heart disease (*25*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of bacillary dysentery and fevers. Also as a haemostat for excessive menstrual or other gynaecological bleeding, and as a tonic (*6*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

Intravenous administration of a 95% ethanol extract of Semen Hippocastani (0.2–0.4 ml/kg body weight) decreased histamine-induced erythema in guinea-pigs (*26*). Intragastric administration of a 30% ethanol extract of the seeds sup-

pressed carrageenan-induced footpad oedema and adjuvant-induced arthritis in rats (at doses of 0.6 and 1.5 ml/kg body weight, respectively) (*27*). Intraperitoneal administration of a saponin fraction isolated from a seed extract exhibited analgesic, anti-inflammatory and antipyretic activities in vivo; the saponin fraction also inhibited prostaglandin synthetase activity in vitro (*28*). Intragastric administration of a hydroalcoholic extract of the seeds to rats (200–400 mg/kg body weight) suppressed footpad oedema induced by peroxide and carrageenan (*29*). Intravenous or oral administration of aescin to rats (0.5–120 mg/kg body weight) inhibited footpad oedema induced by dextran, and granuloma induced by cotton pellet and formalin paper (*30–32*). Intravenous administration of aescin to rats reduced footpad oedema induced by ovalbumin, formalin and dextran (*33*, *34*).

Vasoactive effects

A hydroalcoholic extract of the seeds induced contractions in canine saphenous veins in vitro, and an intravenous bolus (25–50 mg) increased venous pressure in perfused canine saphenous veins in vivo (*29*).

Cutaneous capillary hyperpermeability induced by chloroform, serotonin and histamine also decreased in rats and rabbits after intragastric administration of a hydroalcoholic extract of the seeds (50–400 mg/kg body weight) (*29*). Aescin (5–10 µg/ml) increased the tension of isolated human saphenous veins and rabbit portal veins in vitro. The effect was due to preferential formation of prostaglandin $F_{2\alpha}$ and was reversed by treatment with indometacin (*35*). The vasoactive effects of aescin were investigated in isolated peripheral blood vessels, isolated arteries and veins (constant-flow perfused cat rear paw, isolated perfused carotid artery of the guinea-pig and iliac veins of the pig). Aescin had a biphasic effect on blood vessels: initial transient dilation was followed by increased tone, which was long lasting in isolated arteries and veins, but was transient in isolated peripheral blood vessels (*36*). Aescin has also been shown to inhibit hyaluronidase activity in vitro (IC_{50} 149.9 µmol/l) (*37*). A hydroalcoholic extract of the seeds (250 µg/ml) reduced lipid peroxidation and had radical-scavenging properties (IC_{50} 0.24 µg/ml for superoxide dismutase radicals) (*38*).

Clinical pharmacology

Chronic venous insufficiency and related conditions

Nine placebo-controlled clinical trials (eight double-blind, one single-blind, seven with crossover design) assessed the efficacy of oral administration of a standardized Semen Hippocastani extract (250–600 mg, equivalent to 100–150 mg aescin daily) in a sustained-release form for the symptomatic treatment of patients with chronic venous insufficiency (CVI) (*13–21*). In one study, 96 patients with CVI received the extract over two treatment periods of 20 days each. Symptomatic improvement in skin colour, venous prominence, oedema, dermatosis, and pain, itching and feeling of heaviness in the legs were observed

in the treated patients (*13*). However, the methodology of this study was poor, and no statistical analysis was performed. Two later studies assessed the efficacy of the extract in 212 patients (*19*) and 95 patients (*17*) with CVI, using a numerical scale to rate the severity of symptoms. A significant symptomatic improvement ($P < 0.01$–0.05) in oedema, calf-muscle spasms, pain and feeling of heaviness in the legs was observed in patients treated with the extract (during two treatment periods of 20 days each) (*17*, *19*). The efficacy of the extract was assessed in a double-blind study of 20 female patients (13 with pregnancy-related varicose veins and seven with CVI) during two treatment periods of 14 days each. A significant reduction in leg volume (114 ml in patients with varicose veins and 126 ml in patients with CVI, $P < 0.01$) was demonstrated by water plethysmography in patients treated with the extract (*21*). Another double-blind study assessed the efficacy of the extract in the treatment of 74 patients with CVI and lower-leg oedema. In patients treated with the extract, the leg volume following induction of oedema was reduced from 32 ml to 27 ml (determined by water plethysmography); in the placebo group the leg volume increased from 27 ml to 31 ml (*18*).

Two further studies investigated the effects of the extract on the intravascular volume of the lower-extremity veins and on interstitial filtration (measured indirectly by venous-occlusion or water plethysmography) in patients with CVI (*14*, *20*). In one of the studies, after a single dose of 600 mg extract (equivalent to 100 mg aescin), the transcapillary filtration coefficient decreased by 22%, as compared with a slight increase in the coefficient of the placebo group. This study demonstrated that the extract exerted its action primarily by reducing capillary permeability (*14*). In the other study, patients treated daily with 600 mg extract (equivalent to 100 mg aescin) for 28 days showed a significant reduction in extravascular volume of the foot and ankle ($P < 0.01$), as well as a significant improvement in oedema, and feelings of tension, pain, fatigue and itching of the legs ($P < 0.05$). However, no changes in venous capacity or calf-muscle spasms were observed (*20*).

The efficacy of the extract was assessed in a randomized, parallel, double-blind study of 40 patients with venous oedema due to chronic deep-vein incompetence stage II. Patients received 369–412 mg extract (equivalent to 75 mg aescin) twice daily for 6 weeks. A significant reduction was observed in leg volume (measured by water plethysmography after oedema induction) and leg circumference in the treated group ($P < 0.01$) (*15*). A randomized, single-blind, parallel study compared the efficacy and safety of class II compression stockings with the extract or placebo in 240 patients with CVI. Patients in the treatment group received 300 mg extract (equivalent to 50 mg aescin) twice daily for 12 weeks. The lower-leg volume of the affected limbs decreased by an average of 43.8 ml in patients treated with the extract and by 46.7 ml in patients wearing compression stockings. In the placebo group, the lower-leg volume increased by 9.8 ml. Thus, treatment with the extract or wearing class II compression stockings resulted in similar decreases in lower-leg volume (*16*).

A randomized, double-blind trial compared the efficacy of a standardized extract (360–412 mg, equivalent to 75 mg aescin, twice daily) and oxerutins (1000 mg *O*-(β-hydroxyethyl)-rutinosides twice daily) in 40 patients with CVI and peripheral venous oedema. A reduction in oedema (based on measurement of leg circumference) was observed in both treatment groups (*39*). Another randomized, double-blind study compared the efficacy of a standardized seed extract with oxerutins in the treatment of 137 postmenopausal women with chronic deep-vein incompetence stage II. Following a 1-week placebo run-in, patients were treated daily with either 600 mg extract (equivalent to 100 mg aescin) or 1000 mg oxerutins for 12 weeks, or 100 mg oxerutins for 4 weeks followed by 500 mg oxerutins for 12 weeks. Patients were observed for 6 weeks after treatment; the group treated with 1000 mg oxerutins had the greatest decrease in leg volume (*40*).

A placebo-controlled, double-blind crossover study assessed the effect of a standardized seed extract in the symptomatic treatment of 52 pregnant women with venous insufficiency. Patients were treated with either one capsule containing 300 mg extract (equivalent to 50 mg aescin) or a placebo twice daily for 2 weeks. The extract was superior to the placebo in reducing oedema and symptoms such as leg pain, fatigue and itching. Patients treated with the extract also showed a greater resistance to oedema induction (*41*). The ability of a standardized seed extract to reduce oedema was investigated in a randomized, double-blind, placebo-controlled trial of 30 patients with CVI. A significant reduction in leg circumference was found in the treatment group ($P < 0.05$) as compared to the placebo group ($P < 0.05$) (*42*).

A double-blind placebo-controlled study investigated the effect of a standardized seed extract (one dose of 600 mg, equivalent to 100 mg aescin) on vascular capacity and filtration in the arms and legs of 12 healthy volunteers. Using vein plethysmography, the study showed a decrease in both vascular capacity and filtration coefficient in subjects treated with the extract (*43*). The effect of a standardized seed extract (one dose of 1800 mg) on the flow velocity of venous blood between the instep and the groin was quantitatively determined in 30 patients with varicose veins by the xenon-133 appearance method. Blood flow increased by >30%, with a lasting effect observed after 12 days of treatment. Blood viscosity was also reduced and there was a 73% improvement in subjective complaints (*44*). A randomized double-blind study assessed the effect of a standardized seed extract on lower-leg oedema in 10 healthy volunteers during a 15-hour airflight. A single dose of the extract (600 mg, equivalent to 100 mg aescin) completely prevented or significantly reduced the increase in ankle and foot oedema ($P < 0.05$), determined by measuring the circumference of the ankle and heel before and after flying (*45*). A post-marketing surveillance study of over 5000 patients suffering from CVI demonstrated that treatment with a standardized seed extract (equivalent to 75 mg aescin) twice daily for 4–10 weeks reduced the symptoms of leg pain, fatigue, oedema and itching (*46*). In a multicentre study without controls, 71 patients with CVI were treated daily with a topical gel containing 2% aescin. After

6 weeks of treatment, a significant reduction in ankle oedema (reduction of 0.7 cm in the ankle circumference, $P < 0.001$) and a significant reduction in the symptom score (60%, $P < 0.001$) was reported (*24*). In a postmarketing surveillance study involving over 4000 patients with CVI, treatment with a standardized extract of the crude drug (equivalent to 50 mg aescin) twice daily improved typical symptoms in more than 85% of patients (*47*).

A criteria-based systematic review assessed the randomized, double-blind, placebo-controlled trials of standardized seed extracts for symptomatic treatment of CVI. The data were extracted from the trials in a standardized manner, and the methodological quality and outcome of each trial were assessed by two independent reviewers. In all trials, the extract was shown to be superior to the placebo. Use of the extract was associated with a decrease in lower-leg oedema, and a reduction in the circumference of the calf and ankle. Other symptoms such as leg pain, itching and fatigue were reduced. Results from five comparative trials demonstrated that the extract was as effective as oxerutins, and one of the five trials showed that the extract was as effective as compression therapy (*48*).

Bruises

The efficacy of a topically applied gel containing 2% aescin in reducing the tenderness to pressure haematoma (experimentally induced by injection) was tested in a randomized, placebo-controlled, single-dose study involving 70 healthy volunteers. Based on tonometric sensitivity measurements, the aescin gel significantly reduced the tenderness to pressure haematoma ($P < 0.001$). This effect was seen 1 hour after treatment and lasted for 9 hours (*49*).

Other trials have assessed the efficacy and safety of a topically applied gel containing 2% aescin for the treatment of bruises and sprains (*22*, *23*).

Contraindications

Semen Hippocastani is contraindicated in cases of known allergy to plants of the Hippocastanaceae family.

Warnings

No information available.

Precautions

Drug interactions

Two suspected cases of toxic nephropathy probably due to very high doses of aescin were reported (*50*). Therefore, Semen Hippocastani should not be administered with other drugs known to be nephrotoxic, such as gentamicin.

Carcinogenesis, mutagenesis, impairment of fertility

A 30% ethanol extract of Semen Hippocastani was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100

(200 µl/ml) (*51*). Sodium aescinate had no effect on the fertility of male rats (*52*).

Pregnancy: teratogenic effects

A 40% ethanol extract of Semen Hippocastani was not teratogenic or embryotoxic in rats or rabbits following intragastric administration of 1.6 ml/kg body weight (*53*). Intragastric administration of a 40% ethanol extract of the seeds to rats (100–300 mg/kg body weight) or rabbits (100 mg/kg body weight) was not teratogenic. However, when pregnant rabbits were given 300 mg/kg body weight, a reduction in birth weight was observed (*54*).

Pregnancy: non-teratogenic effects

Semen Hippocastani has been used in clinical trials involving pregnant women with no ill effects (*21*, *41*). However, the drug should not be administered during pregnancy without medical supervision.

Paediatric use

There is no therapeutic rationale for the use of Semen Hippocastani in children.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or nursing mothers. Therefore, Semen Hippocastani should not be administered during lactation without medical supervision.

Adverse reactions

Case reports have indicated gastrointestinal side-effects such as nausea and stomach discomfort (*47*, *55*). Allergic reactions have also been reported (*56*).

Dosage forms

Crude drug and extracts (*7*). Store away from light and humidity (*1*).

Posology

(Unless otherwise indicated)
Daily dosage: 250.0–312.5 mg twice daily of a standardized powdered extract of the crude drug (equivalent to 100 mg aescin) containing 16–20% triterpene glycosides, calculated as aescin (*55*); topical gels containing 2% aescin (*22–24*, *49*).

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Herba Hyperici

Definition

Herba Hyperici consists of the dried flowering tops or aerial parts of *Hypericum perforatum* L. (Clusiaceae) (*1–3*).

Synonyms

Hypericum officinarum Crantz, *Hypericum officinale* Gater ex. Steud., *Hypericum vulgare* Lam. (*4*). Clusiaceae is also referred to as Guttiferae or Hypericaceae.

Selected vernacular names

Balsana, bassan, bossant, common St John's Wort, corazoncillo, dendlu, devil's scourge, echtes Johanniskraut, Eisenblut, erba di San Giovanni, flor de sao joao, fuga daemonum, hardhay, Hartheu, herbe à mille trous, herbe de millepertuis, Herrgottsblut, Hexenkraut, hierba de San Juan, hiperico, hipericon, houfarighoun, iperico, Jageteufel, Johannisblut, Johanniskraut, John's wort, Jottannesort, klamath weed, Konradskraut, Liebeskraut, Lord God's wonder plant, Mannskraft, millepertuis, pelicao, perforata, perforate St John's wort, pinillo de oro, quian-ceng lou, St Jan's kraut, St John's Wort, seiyouotogiri, sint janskruid, tenturotou, Teufelsflucht, Tüpfelhartheu, witches's herb, zwieroboij (*2*, *4–7*).

Geographical distribution

Indigenous to northern Africa, South Africa, South America, Asia, Australia, Europe and New Zealand, and is naturalized in the United States of America (*2*, *7*, *8*). The plant material is harvested at flowering time (*1*).

Description

A herbaceous, aromatic perennial plant, up to 1 m high; glabrous throughout, green or sometimes glaucous. Stems rounded, 2-winged, erect and branched at top. Leaves oval, linear-oblong, broadly elliptic, subcordate, flat or more or less revolute-marginated with pellucid glands and sometimes a number of brown-black glandular dots. Flowers numerous, forming a broadly paniculate, compound cymose inflorescence. Petals oblong to oblong-elliptic, inequilateral with numerous glandular dots. Seed 1 mm long, cylindrical, brown, minutely pitted longitudinally (*2*, *8*, *9*).

Plant material of interest: dried flowering tops or aerial parts

General appearance

Stem glabrous greenish-yellow to brownish-yellow branching, 2-winged, cylindrical with 2 equidistant longitudinal bands. Leaves glabrous, generally sessile, opposite, greenish-grey, oval, 8–35 mm long, with entire margins; laminal margin often more or less revolute-marginated. Brown-black glandular dots sometimes present along the edges; numerous pellucid glands on the entire surface. Flowers, 2 cm in diameter, regular, forming a broadly paniculate, compound cymose inflorescence at top of stem, composed of: 5 green, lanceolate sepals, containing punctiform, black glandular dots on the edges; 5 golden-yellow petals, with numerous glandular dots along margins; and 3 staminal blades, each divided into multiple golden-yellow stamens. Anthers with single, terminal, dark pigment dot. Ovary elongated and conical, parietal placentation, carries 3 styles. Fruits trilocular capsules containing numerous brown, triangular seeds (*1–3*, *9*).

Organoleptic properties

Odour: weak, aromatic, balsamic; taste: bitter, acrid (*9–11*).

Microscopic characteristics

Transverse section of the stem circular and presents 2 lateral edges corresponding to the 2 longitudinal bands. From the exterior inwards are seen: epidermal layer formed of large polygonal cells; continuous collenchymal layer, slightly more developed at the 2 lateral edges; a cortical parenchyma containing crystals of calcium oxalate in the shape of a sea urchin; a ring of continuous phloem, distinct from the xylem, which consists of large vessels and a lignified parenchyma with a visible cambium; and a lacunose medullary parenchyma. Secretory pockets, almost invisible, rarely present in the endoderm. Upper surface of leaf section shows polygonal cells with sinuous, slightly beaded, anticlinal walls; cells of lower surface smaller, anticlinal walls more wavy with frequent paracytic, sometimes anomocytic, stomata; smooth cuticle, thicker on upper surface; straight-walled, elongated epidermal cells of veins occasionally beaded. Dorsoventral surface of leaf consists of a single palisade layer and large oil glands. Midrib shows single, collateral bundle with small area of lignified xylem. Microscopic characteristics of the sepal resemble those of the leaf. Petal narrow, elongated, thin-walled, epidermal cells with straight anticlinal walls on outer surface and wavy on inner surface. Stamen lignified fibrous layer of anther wall; elongated, thin-walled cells of filament with striated cuticle. Pollen grains spherical or elliptical, 20–28 µm in diameter, with 3 germinal pores and smooth exine. Ovary small polygonal cells

with underlying oil glands. Seed testa brown, thick-walled hexagonal cells (*2*, *3*, *9*).

Powdered plant material

Yellowish-green or brownish-green. Leaf fragments abundant, most containing large characteristic hypericin oil glands with brown to red contents. Fragments of leaf epidermis, the adaxial side with thick-walled punctate, slightly sinuate cells, and abaxial side with sinuate cells and paracytic stomata; mesophyll fragments with large secretory pockets which are spherical, bright, containing strongly refractive oil droplets; fragments of palisade parenchyma; stem fragments with reticulate spiral vessels, areolate punctation, long fibres with thick walls, ligneous parenchyma, and small number of thick-walled, characteristically punctate medullary cells; fragments of petals made of elongated rectangular cells with irregular nodulous thickenings, containing numerous yellow droplets and large, round to oval secretory pockets; fragments of anthers; pollen grains 20–28 µm in diameter, smooth spherical or elliptical with 3 germinal pores; clusters of calcium oxalate crystals (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations and thin-layer chromatography for the presence of characteristic compounds (hypericin, pseudohypericin, chlorogenic acid, hyperoside) (*1*, *9–11*). Additionally, a liquid chromatography–mass spectrometry method is available (*12*). The presence of hyperforin and rutin in Herba Hyperici is used to differentiate *Hypericum perforatum* from other *Hypericum* species (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 3% stems with a diameter greater than 5 mm (*1*) and not more than 2% other foreign matter (*1*, *3*).

Total ash

Not more than 7% (*1*).

Acid-insoluble ash

Not more than 2.5% (*9*).

Sulfated ash

Not more than 2.5% (*9*).

Water-soluble extractive

Not less than 12% (*9*).

Loss on drying

Not more than 10% (*1*, *3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

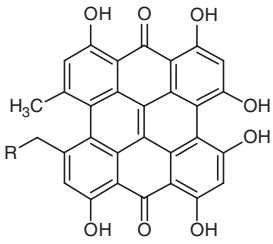
Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

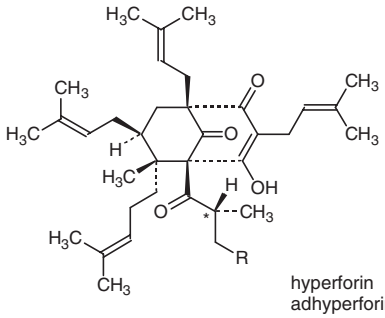
Contains not less than 0.08% hypericins calculated as hypericin, as determined by spectrophotometry (*1*). Quantitation can also be obtained by high-performance liquid chromatography (*2*, *16*).

Major chemical constituents

The major characteristic constituents include 0.05–0.30% naphthodianthrones (hypericin, pseudohypericin, hyperforin, adhyperforin); 2–4% flavonoids (hyperoside, quercitrin, isoquercitrin, rutin); and 7–15% catechin tannins (*2*, *4*, *7*, *17*). The structures of the representative constituents are presented below.

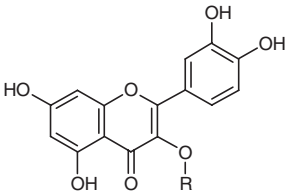


hypericin R = H
pseudohypericin R = OH

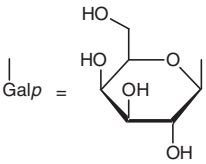


and epimer at C*

hyperforin R = H
adhyperforin R = CH_3

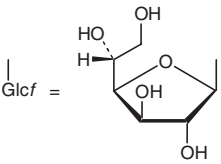


quercitrin R = Rha*p*
hyperoside R = Gal*p*
isoquercitrin R = Glc*f*
rutin R =Rha*p*-(1→6)-Glc*p*



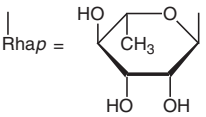
Gal*p* =

β-D-galactopyranosyl



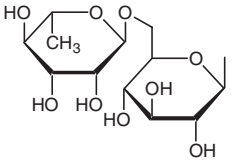
Glc*f* =

β-D-glucofuranosyl



Rha*p* =

6-deoxy-α-L-mannopyranosyl



Rha*p*-(1→6)-Glc*p* =

O -6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

Symptomatic treatment of mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in the *International statistical classification of diseases and related health problems, Tenth revision (ICD-10) (18)*) (*19–31*).

Uses reported in pharmacopoeias and in traditional systems of medicine

Externally for the treatment of minor cuts, burns and skin ulcers (*8*, *32*). Topically for viral infections (*33*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract; treatment of biliary disorders, bladder irritation, the common cold, diabetes mellitus, dyspepsia, haemorrhoids, neuralgia, migraine headaches, sciatica and ulcers (*5*, *8*). Also used as a diuretic, an emmenagogue and an antimalarial agent (*5*, *8*).

Pharmacology

Experimental pharmacology

Antidepressant activity

Behavioural studies, performed primarily in rodents, have demonstrated the antidepressant activity of Herba Hyperici by measuring the exploratory and locomotor activities of animals in an unknown environment (*34*, *35*). Intragastric administration of a 95% ethanol extract of the herb to male gerbils (2 mg/kg body weight) suppressed clonidine-induced depression. Intragastric administration of the extract to male mice (5 mg/kg body weight) enhanced exploratory activity in a foreign environment and significantly prolonged narcotic-induced sleeping time in a dose-dependent manner; the treated mice also exhibited reserpine antagonism. Similar to standard antidepressant drugs, the extract (6 mg/kg body weight) increased the activity of mice in the waterwheel test following a single dose; prolonged administration (6 mg/kg body weight, daily for 3 weeks) decreased aggressiveness in socially isolated male mice (*35*). Intraperitoneal administration of a 50% ethanol extract of the herb to mice (250 mg/kg body weight) reduced the tail flick response to radiant heat, and significantly decreased swimming time in the forced swimming test ($P < 0.05$) and walking time on a rotating rod ($P < 0.005$), as well as exploratory activity ($P < 0.05$) (*36*). Significant, dose-dependent, antidepressant activities were observed in the behavioural despair test and the learned helplessness paradigm in rats treated intragastrically with a carbon dioxide extract of the crude drug containing 38.8% hyperforin (30 mg/kg body weight) or an ethanol extract containing 4.5% hyperforin (300 mg/kg body weight) ($P < 0.001$). The results were comparable to those obtained following intraperitoneal administration of imipramine (10 mg/kg body weight) (*37*). Intragastric administration of an ethanol extract containing 4.5% hyperforin (50, 150 and 300 mg/kg body weight, daily for 3 days) or a carbon dioxide extract devoid of hypericin but containing 38.8% hyperforin (5, 15 and 30 mg/kg body weight, daily for 3 days) had similar antidepressant activity in rodents (rats and mice) (*38*, *39*). In the same dosage range, the ethanol extract potentiated dopaminergic behavioural responses, whereas these effects were either absent or less pronounced in rodents treated with the carbon dioxide extract. In contrast, serotoninergic effects of the carbon dioxide extract were more pronounced than those of the ethanol extract (*38*). Intragastric administration of a methanol extract contain-

ing both hypericin and pseudohypericin (500 mg/kg body weight) to mice produced a dose-dependent increase in ketamine-induced sleeping time and also increased body temperature. The extract also decreased immobility time in the tail suspension test and forced swimming tests, which are both regarded as indicative of antidepressant activity (*40*). Intragastric administration of a 50% ethanol extract of the herb prolonged pentobarbital-induced sleeping time (13.25 mg/kg body weight) and depressed the central nervous system in male mice (25.50 mg/kg body weight). The observed effects were similar to those seen in mice treated with diazepam (2 mg/kg body weight) (*41*). Measurement of some metabolites of biological amines in the urine of various animal models has established a correlation between the excretion in the urine of 3-methoxy-4-hydroxyphenylglycol, the main metabolite of noradrenaline, with the start of the therapeutic antidepressant activity (*42*).

A hydroalcoholic extract of the herb inhibited serotonin (5-hydroxytryptamine, 5-HT) receptor expression in mouse brain synaptosome preparations in vitro (50 µmol/l), and similar effects were observed during ex vivo experiments (*43*). In other studies, hydroalcoholic extracts of the herb inhibited serotonin reuptake (IC_{50} 6.2–25.0 µg/ml) (*44*, *45*), and inhibited both γ-aminobutyric acid (GABA) reuptake (IC_{50} 1 µg/ml) and GABA type A receptor binding (IC_{50} 3 µg/ml) in vitro (*46*).

A hydroalcoholic extract of the fresh flowers and buds of *H. perforatum* (containing 0.1% hypericin) was subjected to a series of assays involving 39 receptor types and two enzymes. Receptor assays exhibiting at least 50% radioligand displacement or 50% inhibition of monamine oxidase (MAO) were considered to be active. The extract demonstrated specific affinity for the GABA (types A and B), serotonin, benzodiazepine and inositol triphosphate receptors, non-specific affinity for adenosine receptors and inhibited MAO types A and B. Purified hypericin lacked any significant MAO (type A or B)-inhibitory activity at concentrations up to 10 µmol/l, and had affinity only for *N*-methyl-D-aspartate (NMDA) receptors in rat forebrain membranes (*47*).

An ethanol extract of the herb inhibited radioligand binding to the NMDA, GABA type A and GABA type B receptors (IC_{50} 7.025, 3.240 and 3.310 µg/ml, respectively). The extract also inhibited synaptosomal GABA and L-glutamate uptake in vitro (IC_{50} 1.11 and 21.25 µg/ml, respectively) (*48*).

A methanol or carbon dioxide extract of the herb, and pure hyperforin significantly inhibited synaptosomal uptake of serotonin, noradrenaline, dopamine, L-glutamate and GABA in vitro (*49*). The carbon dioxide extract (containing 38.8% hyperforin) was more active than the methanol extract (containing 4.5% hyperforin), due to the higher hyperforin concentration. Inhibition was most pronounced with purified hyperforin, showing the following order of affinity: noradrenaline ≥ dopamine > GABA ≥ serotonin >> glutamate (IC_{50} 0.043–0.445 µg/ml) (*49*, *50*). Neither hyperforin nor the carbon dioxide extract inhibited the activity of MAO type A or B at concentrations up to 50 µg/ml (*49*).

A methanol extract of dried *H. perforatum* flowers inhibited radiolabelled-flumazenil binding to the benzodiazepine sites of the GABA receptor in rat brain

preparations in vitro (IC_{50} 6.83 µg/ml) (*51*). The number of serotonergic 5-HT_1 A and 5-HT_2 A receptors significantly increased in the brains of rats treated with an ethanol extract of the herb (2.7 g/kg body weight) daily for 26 weeks, whereas the affinity of both serotonergic receptors remained unaltered. These data suggest that prolonged administration of the extract induced upregulation of the 5-HT_1 A and 5-HT_2 A receptors (*52*). The affinity of hypericin for 30 types of receptor and reuptake sites was determined in vitro. At 1 µmol/l, hypericin inhibited less than 40% specific radioligand binding at all sites tested, except binding at the acetylcholine and sigma receptors (*53*).

The mechanism of the antidepressant effect of Herba Hyperici is not well understood. Early studies focused on the inhibition of MAO and catechol-*O*-methyltransferase (COMT), the two enzymes responsible for the catabolism of biological amines, such as serotonin. Initial investigations analysed the in vitro inhibition of MAO using a series of xanthones isolated from extracts of the herb (*54*, *55*). In later studies, hypericin was reported to inhibit MAO type A (IC_{50} 6.8×10^{-5} mol/l) and type B (IC_{50} 4.2×10^{-5} mol/l) in rat brain mitochondria in vitro (*56*). However, analysis of the hypericin fraction used in these experiments revealed that at least 20% of the extract was composed of other constituents, including some flavonoid derivatives (*8*). Xanthone-containing fractions, free of hypericin and tannins, of a hydroalcoholic extract of *H. perforatum* showed significant inhibition in vitro of MAO type A (which is specific for serotonin) (*57*). In other investigations, only the flavone aglycone, quercitrin, and the xanthone derivative, norethyriol, showed significant inhibition of MAO type A (*57–59*). Hypericin was excluded as the active constituent, and the flavonols and 1,3,6,7-tetrahydroxyxanthone were reported to be the active constituents of a crude extract of the herb (*57–59*). Molecular modelling studies of the constituents of the herb also indicated that the flavonoids may be the most likely candidates for inhibitors of MAO, as their structures are similar to those of known MAO type A inhibitors, toloxotone and brofaromine (*60*).

The MAO-inhibiting activity of six fractions of a hydroalcoholic extract of the herb was determined in vitro and ex vivo. In vitro inhibition of MAO type A in rat brain homogenates could only be shown at a concentration of 1–10 mmol/l of a crude extract or a flavonoid-rich fraction. In ex vivo studies using albino rats, neither the crude extract nor the xanthone-containing fractions inhibited MAO type A or MAO type B after intraperitoneal administration of 300 mg/kg body weight of the extract or 1–10 nmol/l of the fractions. In addition, purified hypericin did not inhibit MAO type A either in vitro or ex vivo (*61*).

The in vitro effects of hypericin, an ethanol extract, and fractions of the extract were tested for inhibition of MAO and COMT obtained from pig liver. Inhibition of MAO was seen with hypericin (1 mmol/l),[1] ethanol extract (0.1 mmol/l),[1] and a fraction containing hypericins and flavonols (0.01 mmol/l).[1]

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

Weak inhibition of COMT was observed with hypericin and the ethanol extract (both at a concentration of 1 mmol/l),[1] whereas two fractions, containing flavonols and xanthones, inhibited COMT to a greater extent at 0.1 mmol/l[1] (*62*). However, the inhibitory concentrations observed during this study appear to be too high to be of any clinical significance.

Other possible mechanisms of the antidepressant effect of Herba Hyperici include its ability to modulate the production of mediators of inflammation such as cytokines, particularly interleukins. Strong suppression of interleukin-6 (IL-6) release was observed in blood samples from depressed patients treated with *H. perforatum* extract (*63*). IL-6 is involved in the modulation of the hypothalamic–pituitary–adrenal (HPA) axis within the nervous/immune system. Elevated IL-6 levels activate the HPA axis, thus increasing levels of adrenal hormones that play a role in depression.

Effect on smooth muscle contraction

A 95% ethanol extract or tincture of the herb (200 µg/ml) inhibited barium- and histamine-induced smooth muscle contractions of guinea-pig ileum in vitro (*64*), and contractions of cat and mouse intestine (*65*). An ethyl acetate extract of the herb (0.1 mg/ml) inhibited potassium chloride- and histamine-induced contractions in pig coronary artery in vitro (*66*).

Antibacterial and antiviral activity

A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus (*MIC 0.31–1.25 mg/ml) (*67*). An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro (*68*, *69*). However, a decoction or hydroalcoholic extract of *H. perforatum* dried stem was not active against herpes simplex virus 1 or 2, or HIV in vitro (100 µg/ml) (*70*). In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus (*71–77*). Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro (*75*, *77–83*). Hypericin inhibited the activity of HIV reverse transcriptase in vitro (IC_{50} 0.77 mmol/l) (*74*, *80*, *84*), and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration (*80–82*). Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus (*85*). Hypericin displayed marginal activity in vitro against Molony murine leukaemia virus and did not show selective activity against herpes simplex

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

virus, influenza virus A, adenovirus or poliovirus (*82*). However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested (IC_{50} 1.56–25 μg/ml), but not against non-enveloped viruses (*82*). The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation (*72*, *75*, *86*).

Protein kinase C inhibition

Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (*87–92*). Hypericin treatment of glioma cell lines inhibited growth and also induced cell death due to protein kinase C (*93*). Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (*89*, *94*). The inhibition of protein kinase C may contribute to the anti-inflammatory effects of Herba Hyperici, as hypericin also inhibited the release of arachidonic acid and leukotriene B4 (*94*).

Wound healing

External application of a 20% aqueous extract of the crude drug to the skin of guinea-pigs and rabbits accelerated healing of experimentally induced wounds (*95*, *96*). Intragastric administration of a 60% ethanol extract of the dried leaves to rats (0.1 ml/animal) accelerated healing of experimentally induced wounds by enhancing the strength and rate of wound contraction and epithelialization (*97*).

Clinical pharmacology

Antidepressant activity

Clinical trials without controls

The safety and efficacy of oral administration of Herba Hyperici has been assessed in more than 5000 patients in numerous case reports and studies (*22*, *23*, *31*, *98*). In a drug-monitoring study involving 3250 patients, 49% were assessed as being mildly depressed, 46% as moderately depressed and 3% as severely depressed at the beginning of the trial. The patients were treated with 300 mg of a dried 80% methanol extract of the herb three times daily, and evaluated after 2 and 4 weeks of therapy. After treatment, 80% of patients had improved or were symptom-free, while 13–16% remained unchanged or were worse. Minor adverse reactions were reported in 2.4% of patients (*31*). A post-marketing trial was performed with 2404 patients with symptoms of mild to moderate depression who were treated with 2–4 capsules of an ethanol extract of the herb (equivalent to 0.6–1.8 mg total hypericin) daily for 4–6 weeks. Symptomatic improvement was evaluated as good to very good in 77% of patients and satisfactory in 15% (*99*).

The effects of an ethanol extract of the herb on the electroencephalogram (EEG) of 40 patients with depression were determined following administra-

tion of the extract (equivalent to 0.5 mg total hypericin or 1.4 g crude drug) daily for 4 weeks. An increase in theta-activity, a decrease in alpha-activity and no change in beta-activity were observed, indicating the induction of relaxation (*100*). A significant increase in nocturnal melatonin plasma concentration was observed in 13 healthy subjects treated with a hydroethanolic extract of the herb (equivalent to 0.53 mg total hypericin) daily for 3 weeks (*101*). A significant increase in the concentration of neurotransmitters in the urine was observed 2 hours after administration of a standardized ethanol extract of the crude drug to six women with symptoms of depression (*42*).

Reviews of clinical trials

The results from over 28 controlled clinical trials involving oral administration of Herba Hyperici have been published. Twelve of the trials, involving 950 patients, were conducted using an ethanol extract of the herb, while the other 16 trials of 1170 patients used a dried 80% methanol extract (*26*). A systematic review and meta-analysis of 23 of the randomized clinical trials involving 1757 patients assessed the efficacy of the herb in the symptomatic treatment of mild to moderate depression. Twenty trials were double-blind, one was single-blind and two were open studies. Fifteen of the trials involving 1008 patients were placebo-controlled and eight studies of 749 patients were comparison trials with other antidepressant drugs. With the exception of two trials, all studies had treatment periods of 4–8 weeks. The daily dosage ranged from 0.4 to 2.7 mg hypericin in 300–1000 mg of a standardized extract of the herb. Seventeen trials used the Hamilton Rating Scale for Depression (Hamilton Depression Rating Scale), which focuses primarily on somatic symptoms, to measure effectiveness, while 12 trials used the Clinical Global Impression Scale. The latter involves observer-rated analysis of severity of illness, global improvement and efficacy. The meta-analysis concluded that the herb was significantly superior to the placebo and was as effective as standard antidepressants such as maprotiline or imipramine (75 mg three times daily). Fewer side-effects were seen in the herb-treated patients (19.8%) than in those receiving standard antidepressants (52.8%) (*21*).

A systematic, criteria-based review of 18 controlled clinical trials using either ethanol or methanol extracts of the herb as a treatment for depression was carried out. Twelve of the trials (nine placebo-controlled and three comparison trials) met the methodological inclusion criteria and were included in the review. The results of the cumulative data show that extracts of the herb were superior to the placebo for the symptomatic treatment of depression as measured by the Hamilton Depression Rating Scale. Results of the comparison studies with maprotiline (75 mg daily) and imipramine (50–75 mg daily) and other standard antidepressants suggest that extracts of the herb have a similar therapeutic profile. Some flaws in the reported studies included no intention to treat analysis, lack of control over compliance, and insufficient description of the extract or placebo used (*19*).

A review of 12 double-blind, placebo-controlled and three comparison clinical trials assessed the efficacy of the herb for the treatment of mild to moderate depression, and the methodology used to perform the studies. The review concluded that the antidepressant activity of a standardized extract of the herb (300 mg standardized to contain 0.9 mg hypericin three times daily for 4–8 weeks) was sufficiently documented. However, it also concluded that no dose-finding studies had been conducted, and that studies on inpatients with severe depression and endogenously depressed patients were lacking. In the three comparison studies, the daily dose of 75 mg maprotiline or 30 mg amitriptyline was viewed as too low. The review concluded that further trials of longer duration in comparison with higher doses of standard antidepressants are warranted (*27*).

A double-blind, randomized, multicentre study was performed to evaluate the efficacy, safety and tolerability of a daily dose of 900 mg hydroalcoholic extract of the herb or 75 mg amitriptyline. After a 1-week placebo run-in phase, 156 patients were treated with 300 mg extract or 25 mg amitriptyline, three times daily for 6 weeks. The patients were assessed before and after treatment. The Hamilton Depression Rating Scale changed from 20 to 10 in the extract-treated patients and from 21 to 6 in the amitriptyline-treated patients ($P < 0.05$). The Montgomery-Asberg Rating Scale for Depression changed from 27 to 13 in the extract-treated patients, and from 26 to 6.5 in the amitriptyline-treated patients ($P < 0.05$). Similar scores in the Clinical Global Impression Scale were observed in both groups (*29*). In a randomized, double-blind, multicentre trial the effectiveness of a standardized dried 80% methanol extract of the herb (containing 0.3% hypericin) was compared with that of imipramine in 209 patients with recurrent depressive disorder, current episode severe without psychotic symptoms (*18*). Patients were treated daily with 1800 mg extract or 150 mg imipramine for 6 weeks. Assessment of patients before and after treatment revealed the following changes. In the Hamilton Depression Rating Scale: from 25.3 to 14.4 in the extract-treated patients, and from 26.1 to 13.4 in the imipramine-treated patients ($P < 0.021$). In the von Zerssen Depression Scale: from 28.9 to 13.6 in the extract-treated patients, and from 26 to 6.5 in the imipramine-treated patients ($P < 0.05$). Results in the Clinical Global Impression Scale showed a trend in favour of imipramine. Although the efficacy of the extract was not significantly different from that of imipramine, analysis of the patient subgroups showed that it was most effective in patients with moderately severe depression (*28*).

A prospective, randomized, double-blind, placebo-controlled, multicentre study assessed the safety and efficacy of a standardized ethanol extract of the herb for the treatment of 151 patients with mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in 1CD-10 (*18*)). Patients received either one 250 mg tablet of the extract (equivalent to 1 mg hypericin) or a placebo twice daily for 6 weeks. The primary efficacy variable was the Hamilton Depression Rating Scale, and secondary variables were the risk–benefit Clinical Global Impression Scales I–III and Visual Analogue Scale

(a validated, patient self-assessment test). Decreases were seen in the Hamilton Depression Rating Scale in 56% of patients treated with the extract, whereas decreases were seen in only 15% of patients who received the placebo (*24*). A randomized, double-blind, placebo-controlled, multicentre study assessed the clinical efficacy and safety of two extracts of the herb differing in their hyperforin content (0.5% or 5.0% hyperforin) in 147 patients suffering from mild to moderate depression as classified in the *Diagnostic and statistical manual of mental disorders*, 4th ed. (DSM-IV) of the American Psychiatric Association (*102*). The patients received either 900 mg of one of the extracts or a placebo daily for 42 days. The patients who received the extract containing 5% hyperforin showed the largest decrease in the Hamilton Depression Rating Scale (a reduction of 10.3; $P = 0.004$, compared to the placebo). A reduction of 8.5 following treatment with the extract containing 0.5% hyperforin and of 7.9 in the placebo-treated group was seen (*20*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers treated with a dried hydromethanolic extract of the herb (300 mg three times daily for 4 weeks) showed improved sleep quality with an increase in deep-sleep phases (*25*). A randomized, double-blind, placebo-controlled study of 54 healthy volunteers evaluated the central pharmacodynamic effects of two extracts of the herb with different hyperforin contents (0.5% or 5.0%) but identical hypericin content. Healthy volunteers received either 900 mg (300 mg three times daily) of one of the extracts or a placebo daily for 8 days. A quantitative topographic electroencephalogram (qEEG) was performed on days 1 and 8 as an indicator of drug-induced pharmacological activity. In both treatment groups, reproducible central pharmacodynamic effects were observed between 4 and 8 hours after administration, and were confirmed on day 8. The extract containing 5% hyperforin showed a marked tendency to produce greater increases in qEEG baseline power performances than the extract containing 0.5% hyperforin. Higher baseline outputs were observed on day 8 in the delta-, theta- and alpha-1 frequencies. Patients treated with the extract containing 5% hyperforin had an increase in qEEG power performance in the delta-frequency after a single dose and in the theta- and alpha-1 frequencies after 8 days of treatment, when compared with placebo treatment (*103*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers were treated with 900 mg (300 mg three times daily) of a dried hydromethanolic extract of the herb for 6 weeks, and the effects on the EEG were assessed. A reduction in alpha-activity and audiovisual latencies in evoked potentials and an increase in beta- and theta-activities were demonstrated (*104*). Another randomized, double-blind, clinical trial of 24 healthy volunteers compared the effects of a dried hydromethanolic extract of the herb with those of maprotiline on the resting EEG and audio-visual latencies in evoked potentials. After 4 weeks of treatment, an increase in theta- and beta-2 activity was observed in patients treated with 900 mg of a standardized hydroalcoholic extract (300 mg three times daily), while a decrease in theta-activity was seen in patients treated with 30 mg maprotiline (10 mg three times

daily) (*105*). The extract also induced an increase of deep sleep as demonstrated by visual analysis of the sleeping phases and automatic analysis of slow-wave EEG activities. Rapid eye movement sleep was not influenced (*25*).

A randomized, single-blind study evaluated the efficacy of the herb for the treatment of seasonal affective disorders (SAD) in conjunction with light therapy. Twenty patients with SAD were treated with 900 mg (300 mg three times daily) of a hydroalcoholic extract of the herb daily for 4 weeks, combined with either bright (3000 lux) or dim light (<300 lux) conditions. Light therapy was carried out for 2 hours daily. A significant reduction of the Hamilton Depression Rating Scale in both groups, but no statistically significant difference between the two groups, was observed (*106, 107*).

Photodynamic effects

The photodynamic effects of hypericin, incorporated into a non-ionic hydrophilic ointment base, were assessed after external application to the skin of patients with herpes communis. The infected dermal surface of treated patients recovered rapidly and the effects lasted in most cases (*33*).

Pharmacokinetics

Single-dose pharmacokinetics of hypericin and pseudohypericin were determined in 12 healthy male volunteers. After a single dose of 300, 900 or 1800 mg extract (equivalent to 250, 750 or 1500 µg hypericin, respectively, and 526, 1578 or 3156 µg pseudohypericin, respectively), plasma levels of the hypericins were measured by high-performance liquid chromatography for up to 3 days. The median plasma levels were 1.5, 4.1 and 14.2 ng/ml for hypericin, and 2.7, 11.7 and 30.6 ng/ml for pseudohypericin, for the three stated doses, respectively. The median half-life of hypericin was 24.8–26.5 hours and 16.3–36.0 hours for pseudohypericin. The median lag-time of absorption was 2.0–2.6 hours for hypericin and 0.3–1.1 hours for pseudohypericin. During long-term dosing (900 mg daily), a steady state was reached after 4 days. The mean maximum plasma level during the steady state was 8.5 ng/ml for hypericin and 5.8 ng/ml for pseudohypericin (*108*).

A randomized, placebo-controlled clinical trial was performed to evaluate the pharmacokinetics and dermal photosensitivity of hypericin and pseudohypericin in 13 healthy volunteers after administration of a single dose of either a placebo or 900, 1800 or 3600 mg of the extract (equivalent to 0.00, 2.81, 5.62 and 11.25 mg total hypericin [combined hypericin and pseudohypericin], respectively). The maximum total hypericin plasma levels observed at 4 hours after administration were 0, 28, 61 and 159 ng/l, respectively. Before and 4 hours after drug intake, the subjects were exposed to increasing doses of solar-simulated irradiation on small areas of their backs. No dose-related increase in light sensitivity was observed. In the multiple-dose analysis, 50 healthy volunteers received 600 mg extract of the herb three times during 1 day only. A slight increase in solar-simulated irradiation sensitivity was observed (*109*).

In a randomized, four-way crossover study without controls involving six healthy volunteers, the pharmacokinetics of hyperforin were determined after administration of single doses of 300, 600, 900 or 1200 mg of an alcohol extract containing 5% hyperforin. The maximum plasma level of hyperforin (150 ng/ml) was reached 3.5 hours after administration of 300 mg of the extract. The hyperforin half-life and mean residence time were 9 and 12 hours, respectively. The pharmacokinetics were linear up to 600 mg of the extract. Increasing the dose to 900 or 1200 mg of extract resulted in values for maximum clearance and area under the curve lower than those expected from linear extrapolation of data from the lower doses (*110*). The pharmacokinetics of hyperforin were studied in nine healthy volunteers, as part of a double-blind, randomized, placebo-controlled study of 54 subjects. The subjects received either a single dose of 900 mg of an alcohol extract containing 5% hyperforin, or 300 mg of an alcohol extract containing 5% hyperforin three times daily for 8 days. No accumulation of hyperforin in the plasma was observed. On the basis of the area under the curve values from the multiple-dose study, the estimated steady-state plasma concentration of hyperforin was approximately 100 ng/ml (*110*).

Contraindications

Herba Hyperici is contraindicated in cases of known allergy to plants of the Clusiaceae family.

Warnings

As with other antidepressant drugs, observation of the therapeutic effects of Herba Hyperici may require 2–4 weeks of therapy. If a significant antidepressant effect is not observed after 6 weeks of treatment, a physician should be consulted.

Precautions

General

Ultraviolet treatments or prolonged exposure to direct sunlight should be avoided when Herba Hyperici is used, as photosensitization may occur in light-sensitive individuals (*32*). (See Adverse reactions.)

Drug interactions

Although the ingestion of foods containing high concentrations of tyramine such as pickled or smoked foods and cheese, and selective serotonin reuptake inhibitors such as fluoxetine are contraindicated with MAO inhibitors, in vivo data linking Herba Hyperici to MAO inhibition are lacking (*111*, *112*). The com-

bination of Herba Hyperici with other standard antidepressant drugs, such as tricyclic antidepressants or fluoxetine, is not recommended, unless under medical supervision.

There are now numerous reports in the medical literature indicating that Herba Hyperici extracts induce hepatic enzymes that are responsible for drug metabolism and may reduce the serum levels and therapeutic efficacy of drugs (*113–117*). Coadministration of theophylline with a Herba Hyperici extract lowered the serum level of theophylline in a patient previously stabilized, requiring an increase in the theophylline dose (*113*). Coadministration of Herba Hyperici and digoxin reduced serum digoxin concentrations after 10 days of treatment (*114*). A decrease in serum cyclosporin, warfarin and phenprocoumon concentrations was seen in patients after they had additionally taken Herba Hyperici extracts (*115*). Concomitant use of Herba Hyperici in five patients previously stabilized on serotonin-reuptake inhibitors resulted in symptoms of central serotonin excess (*116*). The United States Food and Drug Administration has publicized a report concerning a significant drug interaction between Herba Hyperici and indinavir, a protease inhibitor used to treat HIV infections (*117*). Herba Hyperici substantially reduced indinavir plasma concentrations, due to induction of the cytochrome P450 metabolic pathway. As a consequence, the concomitant use of Herba Hyperici and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concentrations, leading to a loss of virucidal activity and the development of resistance (*117*).

Carcinogenesis, mutagenesis, impairment of fertility

The mutagenicity of hydroalcoholic extracts of Herba Hyperici containing 0.2–0.3% hypericin and 0.35 mg/g quercetin has been studied in various in vitro and in vivo systems (*118–121*). The in vitro studies were performed using the *Salmonella*/microsome assay, hypoxanthine guanidine phosphoribosyl transferase test (up to 4 µl/ml), unscheduled DNA synthesis test (up to 1.37 µl/ml), cell transformation test in Syrian hamster embryo cells (up to 10 µl/ml) and spot test in mice (up to 10 µl/ml). The in vivo tests included the chromosome aberration test with bone marrow cells of Chinese hamsters (10 ml/kg body weight, gastric lavage) and the micronucleus test in rodent bone marrow (2 g/kg body weight, gastric lavage). Although some positive results were observed in vitro in the *Salmonella*/microsome assay (*119*, *121*), all the in vivo tests were negative, indicating that the hydroalcoholic extract was not mutagenic in animals. In a 26-week study, intragastric administration of the hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or pre- or postnatal development (*122*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing

mothers; or paediatric use. Therefore, Herba Hyperici should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30–50 times higher than normal therapeutic doses (*123*). Photosensitization in light-sensitive individuals has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet A and B irradiation. Patients were treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24–0.32% total hypericin) three times daily for 15 days. A measurable increase in erythema in light-sensitive individuals was observed after ultraviolet A irradiation. The plasma concentration of hypericin and pseudohypericin in these subjects was double that seen during normal therapeutic treatment of depression (*124*). A single case of reversible erythema after exposure to ultraviolet B has been reported in one patient who had been taking the herb for 3 years (*125*). A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb (*126*). Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks (*21*, *24*, *31*). Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive (*127*, *128*).

Dosage forms

Dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures and drops (*2*, *7*, *32*). Topical preparations include the oil, infusions, compresses, gels and ointments. Store in a well-closed container, protected from light (*10*, *11*).

Posology

(Unless otherwise indicated)

Daily dosage: 2–4 g crude drug (*32*). Internal use: standardized tinctures or fluidextracts (*23*, *98*, *100*), or standardized hydroethanolic or dried hydromethanolic extracts, up to a daily dose of 900 mg extract (equivalent to 0.2–2.7 mg total hypericin) (*19*, *21*, *22*, *27*, *31*).

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Aetheroleum Melaleucae Alternifoliae

Definition

Aetheroleum Melaleucae Alternifoliae is the essential oil obtained by steam distillation of the leaves and terminal branchlets of *Melaleuca alternifolia* (Maiden and Betche) Cheel (Myrtaceae) (*1–3*).

Synonyms

No information available.

Selected vernacular names

Australian tea tree, tea tree (*1–5*).

Geographical distribution

Indigenous to Australia, where it is grown commercially (*6*, *7*).

Description

A narrow-leaved tree not exceeding 6 m. Entire plant glabrous; leaves alternate. Flowers scattered in an interrupted spike; stamens more than 12 mm long united at their bases to form 5 distinct bundles; capsule persisting within fruiting hypanthium (*6–8*).

Plant material of interest: essential oil

General appearance

A colourless to pale-yellow liquid (*1–3*).

Organoleptic properties

Odour: myristic (*1*, *2*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Physico-chemical properties, thin-layer and gas chromatography (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

Chemical

Refractive index: 1.475–1.482 (*1–3*);
Optical rotation: +5° to +15° (*1–3*);
Relative density: 0.885–0.906 (*1–3*);
Solubility in alcohol: soluble in two volumes of 85% ethanol at 20°C (*1–3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

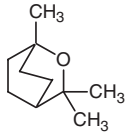
Chemical assays

Contains not less than 30% (w/w) of terpinen-4-ol (4-terpineol) and not more than 15% (w/w) of 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1*, *2*). The oil must contain: not less than 3.5% sabine; 1–6% α-terpinene; 10–28% γ-terpinene; 0.5–12.0% *p*-cymene; not less than 30% terpinen-4-ol; and 1.5–8.0% α-terpineol, as measured by gas chromatography (*1–3*).

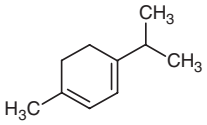
Major chemical constituents

The major constituents are terpinen-4-ol (29–45%), γ-terpinene (10–28%), α-terpinene (2.7–13.0%) and 1,8-cineole (4.5–16.5%) (*8*, *12–15*). Other mono-

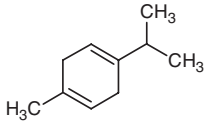
terpenes present in significant quantities (1–5%) include α-pinene, limonene, *p*-cymene and terpinolene. The structures of the major monoterpenes are presented below.



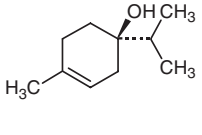
1,8-cineole (eucalyptol)



α-terpinene



γ-terpinene



and enantiomer terpinen-4-ol (4-terpineol)

Medicinal uses

Uses supported by clinical data

Topical application for symptomatic treatment of common skin disorders such as acne, tinea pedis, bromidrosis, furunculosis, and mycotic onychia (onychomycosis), and of vaginitis due to *Trichomonas vaginalis* or *Candida albicans*, cystitis and cervicitis (*16–23*).

Uses described in pharmacopoeias and in traditional systems of medicine

As an antiseptic and disinfectant for the treatment of wounds (*5*).

Uses described in folk medicine, not supported by experimental or clinical data

Symptomatic treatment of burns, colitis, coughs and colds, gingivitis, impetigo, nasopharyngitis, psoriasis, sinus congestion, stomatitis and tonsillitis (*24*, *25*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Aetheroleum Melaleucae Alternifoliae inhibited the growth in vitro of *Escherichia coli*, vancomycin-resistant *Enterococcus faecium*, *Staphylococcus aureus*, metacillin-resistant *Staphylococcus aureus*, and a variety of *Streptomyces* species (MIC 0.04–0.50%) (*26–30*). It also inhibited the growth in vitro of *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Malassezia furfur*, *Candida albicans*, *Cryptococcus neoformans*, *Pityrospermum ovale* and *Trichosporon cutaneum* (MIC 1.1–2.2 mg/ml) (*31–35*). The susceptibility of 32 strains of *Propionibacterium acnes* to the essential oil was determined using a broth dilution method. The MIC was 0.25% for five strains, and 0.50% for the other strains (*36*). Several chemical constituents of the oil, linalool, terpinen-4-ol, α-terpineol,

α-terpinene, terpinolene and 1,8-cineole, inhibited the growth in vitro of a wide variety of microorganisms, including *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* (MIC 0.06–0.50% v/v) (*27*).

Toxicology

The dermal median lethal dose (LD_{50}) of the essential oil in rabbits is >5.0 mg/kg body weight, since 5.0 mg/kg resulted in the deaths of two out of 10 treated rabbits (*37*). The oral LD_{50} in rats is 1.9 g/kg body weight (range of doses 1.4–2.7 g/kg) (*24*, *25*, *37*, *38*). The signs of severe toxicity are respiratory distress, and coma with diarrhoea (*26*, *38*). A few cases of toxicosis after topical application of high doses of the essential oil to dogs and cats have been reported. Symptoms included central nervous system depression, weakness, and lack of coordination and muscle tremors that were resolved within 2–3 days after supportive treatment (*39*).

Clinical pharmacology

Vaginitis and cervicitis

A study without controls assessed the safety and efficacy of a 40% emulsified solution of Aetheroleum Melaleucae Alternifoliae in 13% isopropyl alcohol in the treatment of 130 women with cervicitis or vaginitis due to *Trichomonas vaginalis* or vaginitis due to *Candida albicans*. Intravaginal application of tampons saturated with a 20% emulsified solution healed cervicitis due to *Trichomonas vaginalis* after four weekly treatments. In patients with vaginitis due to *Trichomonas vaginalis*, intravaginal application of a 1% emulsified solution using a saturated tampon, as well as vaginal douching, resulted in clinical cures and restoration of the cervix (*21*). In another study without controls, 28 women with vaginitis due to *Candida albicans* were treated with vaginal pessaries (containing 0.2 g essential oil) every night for 90 days. After 30 days of treatment, 24 patients were already free of symptoms such as leukorrhoea and burning sensation, and 21 were free of *Candida albicans* (*17*).

Cystitis

A randomized, double-blind, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 26 women with chronic ideopathic colibacilli cystitis. Patients were treated with 8 mg essential oil, in an enteric capsule form, orally three times daily for 6 months. After treatment, 54% of the essential oil-treated group were free of symptoms, compared with only 15% in the placebo group. However, approximately 50% of the asymptomatic patients still showed evidence of colibacilli and leukocytes in their urine (*17*).

Acne

A randomized, single-blind, comparison trial evaluated the safety and efficacy of topical application of a gel containing either 5% essential oil or 5% benzoyl

peroxide in the treatment of mild to moderate acne in 119 patients. The results demonstrated that both preparations significantly reduced the number of inflamed and non-inflamed lesions (open and closed comedones) after 3 months of daily treatment ($P < 0.001$), although the onset of action of the gel containing the essential oil was slower than that of the gel containing benzoyl peroxide. Patients treated with the oil-containing gel reported fewer side-effects than those treated with the benzoyl peroxide-containing gel (*16*).

Foot problems

A randomized double-blind, placebo-controlled clinical trial evaluated the efficacy of a cream containing either 10% (w/w) essential oil, 1% tolnaftate or a placebo in the treatment of 104 patients with tinea pedis due to *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*. After application of the cream twice daily for 4 weeks, 30% of the essential oil-treated patients, 85% of the tolnaftate-treated patients and 21% of the placebo-treated patients showed conversion to a negative culture ($P < 0.001$). Both the essential oil-treated group and tolnaftate-treated group demonstrated significant improvement in the clinical symptoms of scaling, inflammation, itching and burning sensation, compared with the placebo group ($P < 0.001$). The cream containing the essential oil reduced symptomatology of tinea pedis as effectively as that containing tolnaftate, but was no better than the placebo in achieving a mycological cure (*22*). A study without controls assessed the efficacy of three products in the treatment of 60 patients with tinea pedis due to *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*, as well as other conditions such as bromidrosis, inflamed corns, calluses, bunions, fissures and mycotic onychia (onychomycosis) of the toenails. Eight patients were treated with 100% essential oil, 40 patients were treated with a 40% emulsified solution of the essential oil in 13% isopropyl alcohol and 12 were treated with an ointment containing 8% essential oil, twice daily for 3 weeks to 4 years. The 100% essential oil was assessed as fair to poor in the treatment of mycotic onychia. The 40% emulsified solution reduced the symptoms of bromidrosis, and inflammation of corns, calluses and bunions. The 8% ointment was effective in the symptomatic treatment of tinea pedis due to *T. mentagrophytes* and *Epidermophyton floccosum*, but was less effective against *T. rubrum* (*23*).

A randomized, double-blind, multicentre comparison trial assessed the efficacy of 100% essential oil or 1% clotrimazole in the treatment of 117 patients with distal subungual mycotic onychia. Patients received twice-daily applications for 6 months, and debridement and clinical assessment were performed at 0, 1, 3 and 6 months. After 3 months, approximately 50% of each group reported improvements. After 6 months, clinical assessment showed partial or full resolution in approximately 60% of each group (*19*).

The efficacy of the essential oil was assessed in an open study of 35 patients with furuncles on the axilla, back, ear, face, forearm, neck and scalp. The furuncles were painted with the essential oil two or three times daily, after thorough

cleaning. In the group treated with the essential oil, only one furuncle required incision, and in 15 patients, the furuncles were completely cured after 8 days of treatment. The only adverse reaction was slight temporary stinging reported by three patients. In the untreated control group, furuncles on five of the 10 patients required incision and the infected site of the furuncles was still apparent after 8 days (*20*).

Contraindications

Aetheroleum Melaleucae Alternifoliae is contraindicated in cases of known allergy to plants of the Myrtaceae family.

Warnings

Not for internal use. Keep out of reach of children (see Adverse reactions).

Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Aetheroleum Melaleucae Alternifoliae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Allergic contact dermatitis after external application and ingestion of Aetheroleum Melaleucae Alternifoliae has been reported (*26*, *40–44*). No adverse reactions were reported in two patch tests using preparations containing up to 5% essential oil (*45*, *46*). Accidental ingestion of 10 ml essential oil caused confusion, disorientation and loss of coordination in a 23-month-old child (*47*). Ingestion of 2.5 ml essential oil by a 60-year-old man resulted in a severe rash and a general feeling of malaise (*48*). Induction of a comatose state lasting 12 hours, followed by 36 hours of a semi-conscious state accompanied by hallucinations, was reported in one patient after ingestion of approximately half a cup (120 ml) of the essential oil. Abdominal pain and diarrhoea lasting up to 6 weeks were also reported (*38*).

Dosage forms

Essential oil (*1*, *2*). Store in a well-filled, airtight container, protected from heat and light.

Posology

(Unless otherwise indicated)

External application of the essential oil at concentrations of 5–100%, depending on the skin disorder being treated (*16–23*).

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Folium Melissae

Definition

Folium Melissae consists of the dried leaves of *Melissa officinalis* L. (Lamiaceae, Labiatae) (*1*, *2*).

Synonyms

Calamintha officinalis Moench. (*3*), *Melissa graveolens* Host, *Thymus melissa* E.H.L. Krause (*4*). Lamiaceae is also referred to as Labiatae.

Selected vernacular names

Alahana, appiastro, badarendjabouya, badranjbuyeh, balm, balm mint, bee balm, blue balm, cedronella, citromfülevél, citronelle, citrounado, citrounela, citrounelo, common balm, cure-all, dropsy plant, erva-cidreira-miuda-de-folha, folia citronellae, franjmeshk, garden-balm, Herzkraut, hhashyshat ennahhl, honey plant, lemon balm, limiera, limouna, limounneta, mallisa, melissa, Melisse, Melissenblätter, Melissenkraut, melisso, melliss, ponciarada, pouncinado, sidrunmeliss, sweet balm, toronjil, toronjil-cidrado, touroudjan, turungan, Zitronenkraut, Zitronenmelisse (*4–8*).

Geographical distribution

Indigenous to western Asia and the eastern Mediterranean region, and is cultivated in central, eastern and western Europe, and the United States of America (*4*, *7*, *8*).

Description

An odorous perennial herb, 0.3–0.9 m high, usually with several stems, lemon-scented on bruising. Stems obtusely quadrangular, furrowed pubescent. Leaves 2–9 cm long and 1–5 cm wide, ovate to obovate-oval, base cuneate truncate or cordate at the base, densely pilose on both surfaces, petiole 0.2–3.5 cm long. Corolla white or pinkish; infundibuliform tube 8–12 mm long; stamens inserted deep in the tube; bracteoles oval-oblong, about 1.5 cm long, pubescent; calyx 5–9 mm long, pubescent outside, pubescent inside (with very short hairs), densely pilose in the middle (*4*, *8*, *9*).

Plant material of interest: dried leaves

General appearance

Leaves oval, cordate, up to about 8 cm long and 5 cm wide, with more or less long petioles; lamina thin, lower surface has conspicuous, raised, reticulate venation; margins roughly dentate or crenate; upper surface bright green, lower surface lighter in colour (*1*).

Organoleptic properties

Odour: aromatic, lemon-like; taste: aromatic, lemon-like (*1*).

Microscopic characteristics

Dorsoventral epidermal cells with sinuous walls and diacytic stomata on lower surface only; very short, conical, unicellular covering trichomes with a finely striated cuticle occur abundantly, especially over the veins on the lower surface; also uniseriate, multicellular (2–5 cells) covering trichomes, wide at the base and narrowing rapidly toward the tip, with slightly thickened, warty walls; secretory trichomes also very abundant, some small with unicellular stalk and unicellular or bicellular head, others large, of laminaceous type, with unicellular stalk and spherical to ovoid head composed of 8 cells (*5*).

Powdered plant material

Greenish. Fragments of the leaf epidermis with sinuous walls; short, conical, unicellular covering trichomes with a finely striated cuticle; uniseriate, multicellular covering trichomes; 8-celled secretory trichomes of laminaceous type, others with unicellular to tricellular stalks and unicellular or, more rarely, bicellular heads; diacytic stomata, on the lower surface only (*1*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for rosmarinic, chlorogenic and caffeic acids (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 2% total foreign matter and not more than 10% of stem fragments with a diameter greater than 1 mm (*1*).

Total ash

Not more than 12% (*1*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

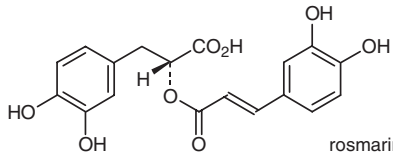
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

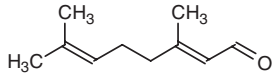
Contains not less than 4.0% total hydroxycinnamic acids calculated as rosmarinic acid (*1*). Quantitative analysis is performed by spectrophotometry at 505 nm (*1*). Essential oil analysis is carried out according to the method described in the *European pharmacopoeia* (*1*).

Major chemical constituents

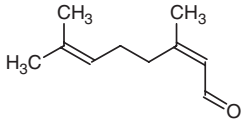
The major characteristic constituents are the hydroxycinnamic acids (rosmarinic [up to 6%], *p*-coumaric, caffeic and chlorogenic acids), and an essential oil (0.02–0.37%) composed of more than 40% monoterpenes and more than 35% sesquiterpenes. The most significant terpenoid components are citral (a mixture of the isomers neral and geranial), citronellal, geraniol, nerol, linalool, farnesyl acetate, humulene (α-caryophyllene), β-caryophyllene and eremophilene. Other constituents include flavonoids, tannins and acidic triterpenes (e.g. ursolic and oleanolic acids) (*4, 6, 7, 13–15*). The structures of the major compound, rosmarinic acid, and terpenoid components are presented below.



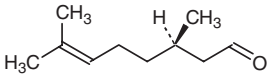
rosmarinic acid



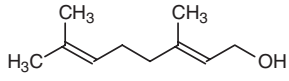
geranial



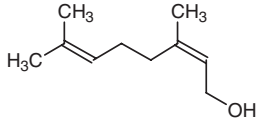
neral



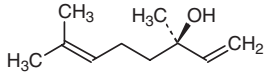
and enantiomer
citronellal



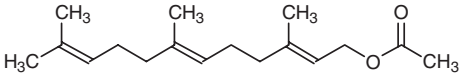
geraniol



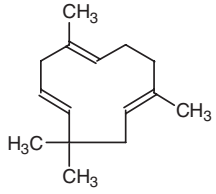
nerol



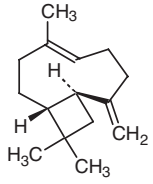
and enantiomer
linalool



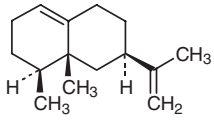
farnesyl acetate



humulene
(α-caryophyllene)



β-caryophyllene



eremophilene

Medicinal uses

Uses supported by clinical data

Externally, for symptomatic treatment of herpes labialis (*16–18*).

Uses described in pharmacopoeias and in traditional systems of medicine

Orally as a carminative for gastrointestinal disorders, and as a sedative for treatment of nervous disturbances of sleep (*5*, *15*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, asthma, bee stings, coughs, dizziness, dysmenorrhoea, migraine headaches, tachycardia, toothache, tracheobronchitis and urinary incontinence (*6*, *19*).

Pharmacology

Experimental pharmacology

Antiviral activity

Aqueous extracts of Folium Melissae inhibited the replication in vitro of herpes simplex virus type 2, influenza virus A_2 (Mannheim 57) and vaccinia virus at a concentration of 10% (*20*). A dried aqueous extract of the leaves inhibited the replication of herpes simplex viruses in vitro at a concentration of 200 µg/ml (*18*). A condensed tannin isolated from an aqueous extract of the leaves inhibited haemagglutination induced by Newcastle disease virus or mumps virus; protected eggs and chick cell cultures from infection by Newcastle disease virus; and prevented haemagglutination by Newcastle disease, mumps and parainfluenza viruses 1, 2 and 3, but not by influenza viruses A and B (*21*). A tannin-free polyphenol fraction of an aqueous extract of the leaves was active against herpes simplex and vaccinia viruses in egg and cell culture systems (*22*). Aqueous extracts of the leaves have also been reported to have activity against Semliki Forest virus, influenza viruses and myxoviruses in vitro (*23*, *24*).

Antispasmodic activity

An ethanol extract of the leaves inhibited histamine- and barium-induced contractions of guinea-pig ileum in vitro (200 µg/ml), while an aqueous extract was inactive (*25*). A 30% ethanol extract did not inhibit acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro at concentrations up to 10 µl/ml (*26*). The essential oil inhibited contractions in guinea-pig ileum, rat duodenum and vas deferens, and rabbit jejunum and aorta in vitro (*27*, *28*). The essential oil also exhibited smooth muscle relaxant activity in guinea-pig tracheal muscle (ED_{50} 22 µg/ml) and in an electrically stimulated ileum myenteric plexus/longitudinal muscle preparation (ED_{50} 7.8 µg/ml) (*29*).

Behavioural effects

Inhalation of the essential oil had a weak tranquillizing effect in mice (*30*).

Clinical pharmacology

An open multicentre study of 115 patients with herpes simplex infections of the skin and transitional mucosa demonstrated that external applications of a 1% lyophilized aqueous extract of Folium Melissae in a cream base reduced

the healing time of herpetic lesions from 10–14 days to 6–8 days (*18*). Treatment with the cream also prolonged the recidivation-free intervals, as compared with other topical virustatic preparations containing idoxuridine and tromantidine hydrochloride (*16*, *18*). A subsequent randomized, double-blind, placebo-controlled study of 116 patients with herpes simplex infections of the skin and transitional mucosa demonstrated a significant reduction in the size of herpetic lesions within 5 days in patients treated with the same cream ($P = 0.01$), as compared with placebo treatment (*17*, *18*).

Contraindications

External use: none. Internal use: see Precautions.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A tincture of Folium Melissae was not mutagenic in vitro (*31*) and alcohol extracts had antimutagenic activity in vitro (*32*).

Pregnancy: teratogenic effects

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Pregnancy: non-teratogenic effects

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Nursing mothers

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during lactation without medical supervision.

Paediatric use

Internal use: no information available. Therefore, Folium Melissae should not be administered internally to children without medical supervision.

Other precautions

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions; pregnancy.

Adverse reactions

No information available.

Dosage forms

Comminuted crude drug; powder, tea bags, dried and fluidextracts for infusions and other galenical preparations (*7*, *14*, *15*). Store in a tightly closed container, protected from light (*1*). Do not store in plastic containers (*7*).

Posology

(Unless otherwise indicated)
Daily dosage for oral administration (for gastrointestinal disorders and as a sedative for nervous disturbances of sleep).

Infusion: 1.5–4.5 g crude drug per cup several times daily as needed (*15*); 45% alcohol extract (1 : 1): 2–4 ml three times daily (*5*); tincture (1 : 5 in 45% alcohol): 2–6 ml three times daily (*14*).

Daily dosage for topical application (for herpes labialis).

Cream containing 1% of a lyophilized aqueous extract applied 2–4 times daily from the appearance of prodromal signs to a few days after the healing of the lesions, for a maximum of 14 days (*14*, *18*).

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Aetheroleum Menthae Piperitae

Definition

Aetheroleum Menthae Piperitae is the essential oil obtained by steam distillation of the fresh overground parts of *Mentha* × *piperita* L. (Lamiaceae) (*1–4*).

Synonyms

Mentha piperita (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*5*, *6*).

Selected vernacular names

Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*5–7*).

Geographical distribution

Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1*, *5*, *8*, *9*).

Description

A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*5*, *8*, *10*).

Plant material of interest: essential oil

General appearance

A colourless, pale yellow or pale greenish-yellow liquid (*1*, *2*).

Organoleptic properties

Odour: characteristic, penetrating; taste: characteristic, pungent, followed by a sensation of cold (*1*, *2*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Thin-layer and gas chromatography for characteristic monoterpene profiles (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Chemical

Acid value: not more than 1.4 (*1*, *2*).
Relative density: 0.900–0.916 (*1–3*).
Refractive index: 1.457–1.467 (*1–3*).
Optical rotation: –10° to –30° (*1–3*).
Solvent solubility: miscible with ethanol (96%), ether and methylene chloride (*1*, *2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

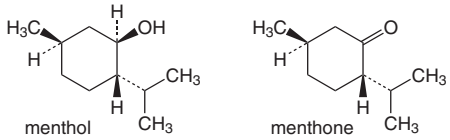
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Chemical assays

The monoterpene content determined by gas chromatography should be 1,8-cineole (6–14%), limonene (1–5%), menthone (14–32%), menthofuran (1–9%), isomenthone (2–10%), menthyl acetate (3–5%), menthol (30–55%), pulegone (not more than 4.0%) and carvone (not more than 1.0%). The ratio of 1,8-cineole to limonene should be greater than 2.0 (*1*, *2*).

Major chemical constituents

The major constituents are menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2*, *6*, *9*, *13*, *14*). The structures of the major monoterpenes, menthol and menthone, are presented below.



Medicinal uses

Uses supported by clinical data

Internally for symptomatic treatment of irritable bowel syndrome (*15–20*), and digestive disorders such as flatulence and gastritis (*21–23*). Externally for treatment of myalgia and headache (*21*, *24–27*).

Uses described in pharmacopoeias and in traditional systems of medicine

Internally and externally for the symptomatic treatment of catarrh and coughs (*21*, *22*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of dysentery, diabetes, dysmenorrhoea, fevers, jaundice and urinary infections (*7*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Aetheroleum Menthae Piperitae inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia*

coli (*28–30*), but did not affect the growth of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (*28*, *30*). The essential oil inhibited the growth in vitro of *Trichophyton equinum* and *T. rubrum* (at a concentration of 0.4 µg/ml) (*31*), *Aspergillus flavus*, *A. fumigatus* and *A. niger* (*32*).

Antispasmodic activity

The essential oil had smooth muscle relaxant activity in guinea-pig ileum (ED_{50} 26.0 mg/l) and trachea (ED_{50} 87.0 mg/l) in vitro (*33*), and inhibited electrically induced contractions of guinea-pig ileum (IC_{50} 0.176 mg/ml) in vitro (*34*). The essential oil decreased both the number and amplitude of spontaneous contractions, and inhibited spasms induced by barium chloride, pilocarpine and physostigmine in isolated segments of rabbit and cat ileum (inhibitory concentrations 0.05 µg/ml) (*35*). The essential oil (0.5 µmol/l) inhibited smooth muscle contractions of guinea-pig ileum in vitro induced by barium chloride, carbachol, histamine and potassium chloride (*36*). Both the essential oil and menthol act as calcium antagonists, since they inhibited the influx of calcium ions through smooth muscle of guinea-pig ileum and taenia coli isolated from humans (*36–39*). The essential oil and menthol inhibited smooth muscle contractions of guinea-pig ileum induced by potassium chloride (IC_{50} 28.1 and 21 µg/ml, respectively) and induced electrically (11.5 and 7.7 µg/ml, respectively) (*40*). Both also inhibited $^{45}Ca^{2+}$ uptake induced by potassium ion-dependent depolarization in brain synaptosomes and retinal neurons, and inhibited specific binding of [^{3}H]nitrendipine to ileal smooth muscle, synaptosomes and retinal neurons (*40*). The essential oil relaxed carbachol-contracted guinea-pig taenia coli (IC_{50} 22.1 µg/ml), and inhibited spontaneous contractions in isolated guinea-pig colon (IC_{50} 25.9 µg/ml) and rabbit jejunum (IC_{50} 15.2 µg/ml) (*41*). The essential oil also attenuated contractile responses in guinea-pig taenia coli induced by acetylcholine, histamine, serotonin (5-hydroxytryptamine) and substance P (*41*). Contraction of Oddi's sphincter induced by morphine was reversed after intravenous administration of the essential oil to guinea-pigs (1.0 mg/kg body weight). However, intravenous injection of the essential oil to guinea-pigs (25 mg/kg body weight) was found to increase spasms of the sphincter (*42*). Intragastric administration of the essential oil exhibited cholagogic activity in rats. This activity was attributed to (–)-menthol, a major constituent of the essential oil (*43*).

Antifoaming activity

The essential oil (0.1%) had antifoaming and carminative activity in vitro; however, the antifoaming effect was less than that observed with a combination of dimethicone and silica (*44*).

Toxicology

Intragastric administration of the essential oil (100 mg/kg body weight) to rats daily for 28 days induced histopathological changes (scattered cyst-like spaces)

in the white matter of the cerebellum. No behavioural or clinical symptoms due to the encephalopathy were observed (*45*).

Clinical pharmacology

Antispasmodic activity

Irritable bowel syndrome

Aetheroleum Menthae Piperitae is a carminative with antispasmodic activity that reduces intracolonic pressure (*22*). In an open study of 20 patients, an aqueous suspension of peppermint oil (British Pharmacopoeia Standard) injected along the biopsy channel of a colonoscope relieved colonic spasms within 30 seconds, allowing easier passage of the instrument or facilitating polypectomy (*16*). The essential oil relaxed the oesophageal sphincter when administered orally (15 drops [about 0.88 ml] oil in 30 ml water), decreasing the pressure differential between the stomach and oesophagus, and allowing reflux to occur (*46*).

In a double-blind, placebo-controlled, crossover clinical trial, 18 patients with symptoms of irritable bowel syndrome were treated daily with three enteric-coated gelatin capsules, each containing either 0.2 ml essential oil or a placebo for 3 weeks. Patients reported feeling significantly better while taking capsules containing the essential oil than when taking those containing placebo ($P < 0.01$) and considered the essential oil significantly better than the placebo in relieving abdominal symptoms ($P < 0.005$) (*19*). These results were confirmed in a later study (*15*). A matched-pair, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 40 patients with symptoms of irritable bowel syndrome. After 14 days of treatment with 1–2 enteric-coated gelatin capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed an increase in intestinal transit time, and subjective improvement in the feeling of fullness, bloating, bowel noises and abdominal pain, as compared with patients who received the placebo (*20*).

Administration of the essential oil to patients undergoing barium enemas relieved the associated colonic spasms (*47, 48*). However, two earlier trials failed to confirm the antispasmodic and analgesic activity of the essential oil in the treatment of irritable bowel syndrome (*49, 50*). A double-blind, placebo-controlled trial assessed the effects of peppermint oil in 34 patients with symptoms of irritable bowel syndrome. After 4 weeks of treatment with two capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed no significant difference in their overall symptoms, as compared with those who received the placebo treatment (*49*).

A prospective, randomized double-blind, placebo-controlled trial assessed the efficacy and safety of enteric-coated capsules containing 0.2 ml essential oil (one capsule 3–4 times daily for 1 month) for the symptomatic treatment of 110 patients with irritable bowel syndrome. After treatment, 79% of patients

in the treatment group and 43% of those in the placebo group experienced alleviation of severe abdominal pain; 83% of the treated group and 32% of the placebo group had reduced abdominal distention and a reduced stool frequency; 73% of the treated group and 31% of the placebo group had fewer bowel noises; and 79% of the treated group and 22% of the placebo group had less flatulence (*17*).

A review of five randomized, double-blind, placebo-controlled clinical trials assessed the efficacy of the essential oil in the symptomatic treatment of irritable bowel syndrome (*18*). By measuring the improvement of symptoms, the meta-analysis showed that two of the trials (*49*, *51*) did not show a significant difference between the essential oil and the placebo. However, three of the trials demonstrated significant improvements in symptoms after treatment with the essential oil (*15*, *19*, *52*). Although there were methodological flaws in most of the trials analysed, the analysis suggested that there was a significant positive effect of the essential oil ($P < 0.001$) on the symptomatic treatment of irritable bowel syndrome, as compared with the placebo (*18*).

Dyspepsia

A double-blind, placebo-controlled multicentre study involving 45 patients with non-ulcer dyspepsia assessed the change in pain intensity and Clinical Global Impression Scale after treatment with an enteric-coated capsule containing a combination of the essential oil (90 mg) and caraway oil (50 mg). After 4 weeks of treatment with the essential oil/caraway oil capsules (one capsule three times daily), 63% of patients were free of pain; 89.5% had less pain; and 94.5% showed improvements in the Clinical Global Impression Scale (*23*). In another study, oral administration of the essential oil (0.2 ml) delayed the gastric emptying time in healthy volunteers and in patients with dyspepsia (*53*).

Analgesic activity

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (peppermint oil) and Aetheroleum Eucalypti (eucalyptus oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; and traces of both peppermint oil and eucalyptus oil; or a placebo. The test preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. The preparations improved cognitive performance, and induced muscle relaxation and mental relaxation, but had no effect on sensitivity to headache (*27*). A randomized, double-blind, placebo-controlled study assessed the efficacy of the essential oil in the treatment of 41 patients suffering from chronic tension headache. At each headache episode, patients were treated orally with two capsules of either paracetamol (1 g) or placebo, or exter-

nal application of 10% essential oil in ethanol, or a placebo solution. Compared with the placebo solution, the 10% essential oil preparation produced a significant ($P < 0.05$) reduction in headache intensity within 15 minutes. Paracetamol was also more effective than the oral placebo but did not differ significantly from topical treatment with the essential oil (*54*).

Contraindications

Preparations of Aetheroleum Menthae Piperitae should not be used internally by patients with inflammation of the gastrointestinal tract or gall bladder, or with impaired liver function (*21*). Hypersensitivity to the essential oil has been reported (*55–57*).

Warnings

Aetheroleum Menthae Piperitae preparations should not be applied to the face, especially the nose, of infants or young children (*21*, *22*). Keep out of reach of children.

Precautions

General

Patients with achlorhydria (due to medication with histamine H_2 receptor antagonists) should only use enteric-coated preparations (*19*, *58*).

Carcinogenesis, mutagenesis, impairment of fertility

Aetheroleum Menthae Piperitae was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA1535 (*59*).

Paediatric use

No information available. Therefore, Aetheroleum Menthae Piperitae should not be administered to children without medical supervision. (See also Contraindications and Warnings.)

Other precautions

No information available on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; or nursing mothers. Therefore, Aetheroleum Menthae Piperitae should not be administered during pregnancy or lactation without medical supervision.

Adverse reactions

Following internal administration of Aetheroleum Menthae Piperitae, gastric complaints have been reported in individuals sensitive to the essential oil (*21*). The use of non-enteric-coated essential oil preparations has occasionally caused

heartburn, especially in patients suffering from reflux oesophagitis (*58*). Skin rashes, headache, heartburn, perianal burning, bradycardia, muscle tremors and ataxia have been reported as rare side-effects, usually associated with overdose (*18*, *56*, *60–65*). Recurrent muscle pain has been associated with the ingestion of the essential oil (*66*). Following external administration of Aetheroleum Menthae Piperitae, skin irritation has been reported (*58*).

Dosage forms

Essential oil, concentrated peppermint emulsion, peppermint spirit and other galenic preparations (*1*, *21*). Store in a well-closed container, protected from light (*1*, *2*).

Posology

(Unless otherwise indicated)

Internal use

For digestive disorders, daily dosage: 0.2–0.4 ml essential oil three times daily in dilute preparations (*58*, *67*) or suspensions (*19*). By inhalation: 3–4 drops essential oil in hot water (*21*). Lozenges: 2–10 mg essential oil per lozenge (*58*).

For irritable bowel syndrome, daily dosage: 0.2–0.4 ml essential oil three times daily in enteric-coated capsules (*21*, *58*).

External use

5–20% essential oil in dilute, semisolid or oily preparations; 5–10% essential oil in aqueous-ethanol; nasal ointments containing 1–5% crude drug (*21*).

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Folium Menthae Piperitae

Definition

Folium Menthae Piperitae consists of the dried leaves of *Mentha* × *piperita* L. (Lamiaceae) (*1–3*).

Synonyms

Mentha piperita (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*1*, *4*).

Selected vernacular names

Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*1*, *4*, *5*).

Geographical distribution

Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1*, *3*, *6*, *7*).

Description

A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*1*, *7*, *8*).

Plant material of interest: dried leaves

General appearance

Green to greenish-brown. Leaves whole, broken or cut; thin, fragile; whole leaf 3–9 cm long and 1–3 cm wide, often crumpled. Lamina oval or lanceolate; apex acuminate; margin sharply dentate; base asymmetrical. Venation pinnate,

prominent on the lower surface, with lateral veins leaving the midrib at an angle of about 45°. Lower surface slightly pubescent and secretory trichomes visible under a hand lens as bright yellowish points. Petiole grooved, usually up to 1 mm in diameter and up to 1 cm long (*2*).

Organoleptic properties

Odour: characteristic, penetrating; taste: characteristic, aromatic (*2*).

Microscopic characteristics

Upper epidermis composed of large, clear epidermal cells with sinuous, vertical walls and possessing few or no stomata, few glandular trichomes present; palisade parenchyma, comprising a layer of columnar cells rich in chloroplasts; spongy parenchyma, of 4–6 layers of irregularly shaped chloroplastid-containing cells and intercellular air-spaces. Lower epidermis of small epidermal cells with sinuous, vertical walls and numerous diacytic stomata; in the region of veins and midrib, exhibits non-glandular and glandular trichomes as outgrowths; non-glandular trichomes uniseriate, papillose, 1–8-celled; glandular trichomes have 1–2-celled stalk and 1–8-celled glandular head containing the essential oil. Calcium oxalate crystals absent; pollen grains spheroidal and smooth (*1*, *4*, *7*, *8*).

Powdered plant material

Brownish-green. Fragments of leaf tissue with cells of epidermis having sinuous walls, cuticle striated over the veins, diacytic stomata present predominantly on the lower epidermis; epidermis fragments from near leaf margin with isodiametric cells showing distinct beading and pitting in anticlinal walls; covering trichomes short, conical, unicellular, bicellular or elongated, uniseriate multicellular (3–8 cells) with striated cuticle. Glandular trichomes of 2 types: either with unicellular base with small, rounded, unicellular head 15–25 µm in diameter; or with unicellular base with enlarged, oval multicellular head 55–70 µm in diameter composed of 8 radiating cells; dorsoventral mesophyll fragments with a single palisade layer and 4–6 layers of spongy parenchyma; yellowish crystals of menthol under the cuticle of secretory cells. Calcium oxalate crystals absent (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography (*1*, *2*). Gas chromatography of the steam-distilled essential oil (*9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 5% stems, the diameter of which must be not more than 1.5 mm; not more than 8% leaves showing brown stains due to *Puccinia menthae* (*2*); not more than 2% other foreign matter (*2*).

Total ash

Not more than 15% according to the *European pharmacopoeia* (*2*); not more than 12% according to the *African pharmacopoeia* (*1*).

Acid-insoluble ash

Not more than 1.5% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*11*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Sulfated ash, water-soluble extractive, alcohol-soluble extractive, and loss on drying tests to be established in accordance with national requirements.

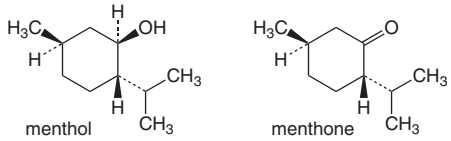
Chemical assays

Whole and cut leaves contain not less than 1.2% and 0.9% (v/w) essential oil, respectively, determined as described in the *European pharmacopoeia* (*2*).

Major chemical constituents

The major constituent of the leaves is the essential oil (0.5–4%), which contains menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2*, *4*, *6*, *12*, *13*).

The structures of the major monoterpenes, menthol and menthone, are presented below.



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Symptomatic treatment of dyspepsia, flatulence and intestinal colic (*1*, *3*, *14*, *15*).

Uses described in folk medicine, not supported by experimental or clinical data

As an emmenagogue, vermifuge, lactation enhancer and sedative. Also used to treat bronchitis, bacillary dysentery, diabetes, diarrhoea, dysmenorrhoea, fevers, hypertension, jaundice, nausea, pain, and respiratory and urinary tract infections (*5*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Extracts of Folium Menthae Piperitae have antibacterial and antiviral activity in vitro. Addition of ground leaves to the agar medium inhibited the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* at concentrations of 0.1–2.0% (w/v) (*16*). Aqueous and ethanol extracts of the leaves reduced the number of plaques of the rinderpest virus at concentrations of 4–8 mg/ml (*17*). Aqueous extracts of the leaves demonstrated activity against the following viruses in egg and cell culture: Newcastle disease, herpes simplex, vaccinia, Semliki Forest and West Nile (*18*).

Smooth muscle contraction

A 31% ethanol extract of the leaves inhibited both acetylcholine- and histamine-induced smooth muscle contractions in guinea-pig ileum in vitro at a concentration of 10 ml/l (*19*, *20*). The results were similar to those obtained with 0.13 mg atropine (*19*). An aqueous flavonoid fraction isolated from a leaf

extract inhibited barium chloride-induced muscle contractions of guinea-pig ileum in vitro at a concentration corresponding to 0.5 g leaves/ml (*21*).

Choleretic activity

Injection of a leaf infusion (0.5 ml) or a flavonoid fraction (equivalent to 3.3 g leaves/kg body weight) increased the amount of bile acids in cannulated rats and dogs (dose 0.4 mg/kg body weight) (*21*, *22*). A mixture of flavonoids, isolated from the leaves, had choleretic activity in dogs (2 mg/kg body weight) (*23*). Flavomentin, a flavonoid isolated from the leaves, stimulated bile secretion and the synthesis of bile acids in dogs (2 mg/kg body weight) (*24*). Intragastric administration of a 30% ethanol extract of the leaves to rats (1 ml/kg body weight) increased bile flow by 43%. The extract did not induce sedation in mice at doses up to 10 ml/kg body weight (*20*).

Anti-oedema activity

Topical application of a methanol leaf extract to mice (2.0 mg/ear) inhibited ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*25*).

Analgesic activity

Intragastric administration of a 30% ethanol extract of the leaves inhibited phenylbenzoquinone-induced writhing in mice (ED_{50} 2.1 ml/kg body weight) (*20*).

Toxicology

Intragastric administration of a leaf extract (50 g leaves infused with 500 ml hot water for 10 minutes, then spray-dried) to 12 mice (4 g/kg body weight as a single dose) did not result in central nervous system depression, toxic effects or mortality (*26*).

Clinical pharmacology

None.

Contraindications

No information available.

Warnings

No information available.

Precautions

General

Patients with gallstones should not use Folium Menthae Piperitae unless under medical supervision (*15*).

Other precautions

No information available on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium Menthae Piperitae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

No information available.

Dosage forms

Dried leaves (*2*, *3*). Tincture and infusions (*6*). Store in a well-closed container, protected from light (*2*).

Posology

(Unless otherwise indicated)
Daily dosage: 1–3 g crude drug three times daily (*14*, *27*). Infusion: pour 150 ml hot water over 1.5–3.0 g (one tablespoon) dried leaves, steep for 10 minutes, strain and drink three times daily between meals (*6*, *15*, *28*). Tincture: 2–3 ml (1:5, 45% ethanol) three times daily (*14*).

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Folium Ocimi Sancti

Definition

Folium Ocimi Sancti consists of the fresh or dried leaves of *Ocimum sanctum* L. (Lamiaceae) (*1–3*).

Synonyms

Moschosma tenuiflorum (L.) Heynhold, *Ocimum album* Blanco, *O. anisodorum* Muell., *O. brachiatum* Hasskarl, *O. flexuosum* Blanco, *O. frutescens* Burm., *O. gratissimum* Lour., *O. inodorum* Burm., *O. monachorum* L., *O. nelsonii* Zipp ex Span., *O. tenuiflorum* L., *O. virgatum* Blanco (*4*).

Selected vernacular names

Badrooj, basilic des moines, bazsalikom levél, daun lampes, garden balsam, green tulsi, holy basil, huong nhu tịa, jagu lu myah, kamimebouki, kaphrao, kaprao, kemangi, kemangi laki, kra phrao, lampas, monk's basil, peihan, rayhhan, reihan, sacred basil, saling-kugon, saling-kugon ma, selaseh puteh, solasi, sulasi, sursa, tamole, thulasi, tjlsi, tulashi, tulasi, tulsi (*1*, *4–9*).

Geographical distribution

Indigenous to India and parts of north and eastern Africa, Hainan Island and Taiwan, China. It is cultivated in south-east Asia (*6*, *8*, *10*).

Description

A herb or shrub, up to 1 m high, often much branched. Stem square, lower parts sub-serrate, higher parts slightly furrowed and more densely pubescent or sub-glabrous. Leaves simple, opposite, oblong, ovate or oval-oblong, 2.7–7.5 cm long, 1–3 cm wide, with acute top, cuneate, obtuse to rounded base, margin entire, undulate or serrate, both surfaces thinly pubescent and dotted; petiole 0.2–3.0 cm long. Calyx 0.2–0.4 cm long, with or without long or short hairs, ciliate, densely glandulose; upper lip 2.0–3.5 mm long, oval short-acuminate; lower lip 1.0–2.5 mm long, dentate, teeth linear-acuminate from an equal- or unequal-sided triangular to ovate base, 2 anterior teeth equalling or slightly surpassing the upper lip; fruiting calyx not completely closed by teeth. Upper part of the corolla villous and glandulose in the upper part; lobes of upper lip

rounded, lobes of lower lip obtuse to rounded. Nutlets obovoid, dark brown or black, 1–2 mm long; pericarp swells into a slimy mass when moistened (*6*, *8*, *11*, *12*).

Plant material of interest: fresh or dried leaves

General appearance

Leaves green to greenish-brown, 2.5–7.5 cm long, 1–3 cm wide, oblong, ovate or oval-oblong, with acute top, cuneate, obtuse to rounded base, pinnate veins, serrate or entire and undulate margin; thin but fleshy, both surfaces thinly pubescent; petiole cylindrical, 1–2 cm long, thinly pubescent (*1*).

Organoleptic properties

Odour: characteristic, aromatic; taste: slightly pungent (*1*, *2*).

Microscopic characteristics

Transverse section of the leaf through its midrib: upper epidermis consists of a layer of small, quadrangular transparent cells with thin walls and thin smooth cuticle. On tangential view, these cells are polygonal with straight or wavy walls. Lower epidermis consists of a layer of small, quadrangular transparent cells with thin walls and thin smooth cuticle. Trichomes bent, consisting of 2–6 cells; glandular trichomes short, Lamiaceae type, consisting of 1 stalk cell and 2–4 cells with rounded heads. Palisade parenchyma consists of layer of long cylindrical cells containing chlorophyll; spongy parenchyma consists of polygonal cells with thin, straight or slightly wavy side walls. Vascular bundles collateral type with collenchyma cells. Stomata diacytic, on upper and lower epidermis (*1*).

Powdered plant material

Upper epidermis with diacytic stomata, glandular trichomes and palisade cells; lower epidermis with diacytic stomata and underlying spongy cells; 2- and 4-celled glandular trichomes; uniseriate, multicellular trichomes with collapsed cells; lignified fibres; spiral vessels; pollen grains rare; parenchyma and collenchyma from petioles (*2*).

General identity tests

Macroscopic and microscopic examinations (*1*), and thin-layer chromatography (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Total ash

Not more than 13% (*1*).

Acid-insoluble ash

Not more than 1% (*1*).

Sulfated ash

Not more than 20% (*2*).

Water-soluble extractive

Not less than 5% (*1*).

Alcohol-soluble extractive

Not less than 5.0% (*2*).

Loss on drying

Not more than 14% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

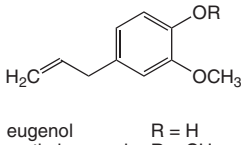
Chemical and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 0.5% essential oil (*3*). Gas chromatography and gas chromatography–mass spectroscopy methods are available for qualitative and quantitative determination of volatile constituents (*16*).

Major chemical constituents

The main components are tannins (4.6%) and essential oil (up to 2%) (*1*). The amounts of the primary constituents of the essential oil vary according to the geographical distribution and variety of the source plant material: eugenol (up to 62%), methyleugenol (up to 86%), and α- and β-caryophyllene (up to 42%). Also present are methylchavicol, linalool and 1,8-cineole (*4*, *16–19*). The structures of the major constituents are presented below.



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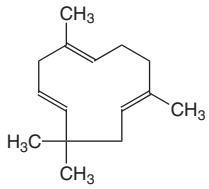
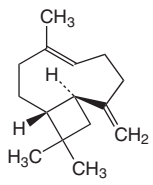
methyleugenol R = CH_3



α-caryophyllene



β-caryophyllene

Medicinal uses

Uses supported by clinical data

None. Although there are some preliminary clinical data supporting the use of Folium Ocimi Sancti for the treatment of diabetes, further trials are needed to substantiate the data.

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of arthritis, asthma, bronchitis, common cold, diabetes, fever, influenza, peptic ulcer and rheumatism (*1*, *8*, *20*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of earache, epilepsy, heart disease, malaria, sinusitis, snake bites, stomach ache and vomiting. Also as an anthelminthic, to stimulate lactation, to prevent hair loss, and as a tonic (*7*).

Pharmacology

Experimental pharmacology

Analgesic activity

Intraperitoneal or intragastric administration of the fixed oil to mice (3 ml/kg body weight) significantly inhibited writhing induced by acetic acid ($P < 0.01$) (*21*). Intragastric administration of an aqueous suspension or a methanol extract of the leaves to mice (100 mg/kg body weight) showed analgesic activity in the hot-plate test (*22*).

Antispasmodic activity

A 50% ethanol extract of the leaves inhibited histamine-induced bronchospasms and pre-convulsive dyspnoea in guinea-pigs when administered by gastric lavage (200 mg/kg body weight) (*23*, *24*). Intragastric administration of the leaf essential oil or fixed oil to guinea-pigs (0.5 ml/kg body weight) inhibited bronchospasms induced by both histamine and acetylcholine, and pre-convulsive dyspnoea (*23*–*25*).

A hydroalcoholic extract of the leaves inhibited muscle spasms induced by histamine in guinea-pig ileum, and muscle spasms induced by acetylcholine, barium and histamine in guinea-pig small intestine in vitro (*26*). However, an aqueous extract showed no activity in either test system (*27*). In another study, aqueous extracts of the leaves inhibited muscle spasms induced by acetylcholine, histamine and carbachol in rabbit intestine in vitro (*28*).

Antimicrobial activity

An ether or 95% ethanol extract of the leaves inhibited the growth in vitro of *Staphylococcus aureus* and *S. citreus* (*29*, *30*) and of *Mycobacterium tuberculosis* (*29*, *31*). A hot aqueous extract of the leaves inhibited the growth in vitro of *Trichophyton mentagrophytes* (*32*), and the growth of *Aspergillus fumigatus* and *A. niger* was inhibited in vitro when grown on agar plates containing the powdered leaves (*33*).

Anti-inflammatory activity

Intragastric administration of a hydroalcoholic extract of the leaves or the essential oil to rats and guinea-pigs (10 ml/kg body weight) inhibited footpad oedema induced by histamine, serotonin and carrageenan (*23*, *24*). Intragastric administration of the fixed oil and linolenic acid extracted from the leaf to rats inhibited footpad oedema induced by prostaglandin E_2, leukotriene, carrageenan and arachidonic acid (*34*). Intragastric administration of an aqueous leaf extract to rats (100 mg/kg body weight) inhibited footpad oedema induced by croton oil and carrageenan (*22*). Intraperitoneal administration of an aqueous leaf extract to rats (100 mg/kg body weight) also inhibited carrageenan-induced footpad oedema (*35*). A hydroalcoholic extract of the leaves inhibited the activity of prostaglandin synthetase by 88% in vitro at a concentration of 750 µg/ml (*36*). An aqueous leaf extract exhibited anticholinergic and antihistamine activity in guinea-pig ileum and small intestine in vitro (0.15 mg) (*27*).

Antipyretic activity

Intragastric administration of a methanol leaf extract to rats (250 mg/kg body weight) suppressed fever induced by typhoid vaccine (*35*). However, intragastric administration of a hydroalcoholic extract of the leaves to rabbits (10 mg) did not suppress fever induced by yeast (*37*).

Effect on sleeping time

Intraperitoneal administration of an aqueous or 70% ethanol extract (30–40 mg/kg body weight) of the leaves to mice potentiated sleeping time induced by hexobarbital and pentobarbital (*28*, *38*).

Immunostimulatory activity

Intragastric administration of an aqueous or methanol extract of the leaves to rats (100–500 mg/kg body weight) increased antibody titre in both sheep erythrocyte and Widal agglutination tests, thus demonstrating stimulation of the humoral immune response. The cellular immune response was also stimulated, as an increase in lymphocytosis and E-rosette formation was also seen (*39*). Intragastric administration of a leaf essential oil to rats (100 mg/kg body weight) enhanced the titres of both anti-sheep red blood cell and IgE antibodies (*40*).

Endocrinological effects

The effects of a leaf extract on changes in serum triiodothyronine, thyroxine and cholesterol concentrations have been investigated in mice. After 15 days of treatment (0.5 g/kg body weight, by gastric lavage), significant decreases were observed in serum thyroxine concentration, hepatic lipid peroxidation and hepatic glucose-6-phosphate activities. No marked change in serum triiodothyronine levels was noted. The activities of superoxide dismutase and superoxide catalase were increased (*41*).

Antiulcer activity

Intragastric administration of an ethanol extract of the leaves to rats reduced the concentration of plasma corticosterone, which had risen following 30 minutes of noise (100 dB), to normal levels (*42*). An organic solvent extract of the leaves had significant antioxidant activity in a variety of in vitro systems (*43*). Intragastric administration of a 70% ethanol extract of the leaves to rats (100 mg/kg body weight) prevented ulcers induced by acetylsalicylic acid and stress (*44*). Administration of the dried leaves to rats similarly prevented ulcers induced by cold and acetylsalicylic acid (*45*). However, intragastric administration of a methanol extract of dried leaves to mice (2 g/kg body weight) did not prevent stress-induced ulcers (*46*).

Hypoglycaemic activity

Intragastric administration of a 50% ethanol extract of the leaves (250 mg/kg body weight) to albino rats with experimentally induced hyperglycaemia reduced blood glucose levels by 30% (*26*, *47*). Intragastric administration of the leaves (50–400 mg/kg body weight) to rats with diabetes induced by streptozocin resulted in a reduction in blood glucose levels measured after fasting (*48*).

Toxicity

Intragastric administration of eugenol (400–600 mg/kg body weight) has been reported to produce liver damage in mice, whose livers were experimentally depleted of glutathione (*49*). It was also cytotoxic in isolated rat hepatocytes (*50*). However, no generalized toxicity was reported in mice after a 50% ethanol extract of the leaves was injected either intraperitoneally (1 g/kg body weight) (*26*) or intradermally (10 g/kg body weight) (*51*).

Clinical pharmacology

Asthma

In a study without controls, oral administration of an aqueous extract of dried Folium Ocimi Sancti to 20 patients with asthma increased lung vital capacity and relieved laboured breathing (*52*).

Glucose and cholesterol levels

A randomized, placebo-controlled, single-blind, crossover study assessed the effects of the dried leaves on the levels of blood glucose and serum cholesterol in 40 non-insulin-dependent diabetic patients. Patients received orally 2.5 g leaves daily for 4 weeks. Blood glucose levels, measured after fasting and eating, decreased by 17.6% and 7.3% respectively. Mean total cholesterol levels also decreased slightly (by 6.5%) during the treatment period (*20*). No adverse effects were observed.

Contraindications

There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti (*53*, *54*). The use of Folium Ocimi Sancti is therefore contraindicated during pregnancy and lactation.

Warnings

No information available.

Precautions

Drug interactions

One study has shown that eugenol may be hepatotoxic in mice with glutathione-depleted livers (*49*). Therefore, Folium Ocimi Sancti should be used with caution in patients taking drugs such as paracetamol (acetaminophen) that deplete glutathione.

Carcinogenesis, mutagenesis, impairment of fertility

A hot aqueous extract of fresh Folium Ocimi Sancti was not mutagenic in *Bacillus subtilis* H-17 (*rec*+) and M-45(*rec*–) at a concentration of 0.5 ml/disc (*55*).

Intragastric administration of the leaves prevented implantation of the embryo in various animal models (*54*, *56*). Intragastric administration of the leaves (10% of feed) to male mice inhibited spermatogenesis (*57*, *58*).

Pregnancy: teratogenic effects

There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti. In one study, a benzene leaf extract was neither teratogenic nor embryotoxic when administered intragastrically to rats (200 mg/kg body weight) (*53*). However, another study demonstrated that aqueous or benzene extracts of the leaves were embryotoxic when administered intragastrically to rats (100–200 mg/kg body weight) (*54*). (See also Contraindications.)

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions or paediatric use. Therefore, Folium Ocimi Sancti should not be administered to children without medical supervision.

Adverse reactions

No adverse reactions have been reported in clinical trials (*20*, *52*).

Dosage forms

Crude drug and preparations thereof (*1*).

Posology

(Unless otherwise indicated)
Daily dosage: 6–12 g crude drug as a decoction (*8*).

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Oleum Oenotherae Biennis

Definition

Oleum Oenotherae Biennis is the fixed oil obtained from the seeds of *Oenothera biennis* L. (Onagraceae).

Synonyms

Oenothera communis Léveillé, *Oenothera graveolens* Gilib., *Onagra biennis* Scop., *Onagra vulgaris* Spach. (*1*).

Selected vernacular names

Enotera, evening primrose, hhashyshat el hhimar, king's cureall, la belle de nuit, ligetszépeolaj, mematsuyoigusa, Nachtkerzenöl, onagre, raghan-e gole magrebi, teunisbloem (*1–7*).

Geographical distribution

Indigenous to Europe and is naturalized in North America (*7*, *8*).

Description

A biennial or occasionally an annual, up to 1.25 m high. Thick yellowish conical root produces compressed rosettes of obtuse basal leaves, from which arise much-branched reddish, rough stems; stems bear alternate, lanceolate to ovate, entire, 4 cm long, short petioled leaves. Flowers very fragrant, 3–5 cm in diameter, yellow, erect on spikes, 4-petalled; open in the evening and wilt after 1 night. Seed pods contain many small reddish-brown seeds. Plant hybridizes easily (*2*, *9*).

Plant material of interest: fixed oil obtained from the seeds

General appearance

A light-amber liquid.

Organoleptic properties

Odourless; taste: oily.

General identity tests

Standard methods for analysis of fatty acids (*1*, *9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Chemical

Refractive index: 1.476–1.480 (*5*).
Specific gravity: 0.920–0.930 (*5*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

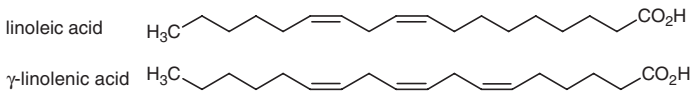
Foreign organic matter acid values to be established in accordance with national requirements.

Chemical assays

Concentration limits of linoleic acid (*cis*-linoleic acid) and γ-linolenic acid (*cis*-γ-linolenic acid) need to be established. However, based on literature data, values of not less than 60% and 7%, respectively, may be considered. A gas chromatography method is available for quantitative analysis (*13*).

Major chemical constituents

The major constituents are linoleic acid (*cis*-linoleic acid) (65–80%), γ-linolenic acid (*cis*-γ-linolenic acid) (8–14%), oleic acid (6–11%), palmitic acid (7–10%) and stearic acid (1.5–3.5%). Other constituents include sterols and triterpene alcohols (*1*, *3*, *6*, *14*, *15*). The structures of linoleic acid and γ-linolenic acid are presented below.



Medicinal uses

Uses supported by clinical data

Internally for symptomatic treatment of atopic eczema (*2*, *16–21*), diabetic neuropathy (*22*, *23*), and mastalgia (*24–26*). Clinical evidence for its use in the treatment of rheumatoid arthritis (*27–30*) is conflicting, as are the results of trials in women with premenstrual syndrome (*31–35*). Further well-designed clinical trials are needed to clarify these data. The results from clinical trials do not support the use of Oleum Oenotherae Biennis for the treatment of climacteric symptoms or psoriasis (*36*, *37*).

Uses described in pharmacopoeias and in traditional systems of medicine

Topical use for the treatment of minor bruises and wounds (*2*).

Uses described in folk medicine, not supported by experimental or clinical data

Taken internally for the treatment of asthma, coughs, gastrointestinal disorders, pain and whooping cough (*2*, *9*, *38*).

Pharmacology

Experimental pharmacology

Anti-allergic activity

Oleum Oenotherae Biennis was added to the diet (1 g/kg body weight, for 5 days) of guinea-pigs sensitized to ovalbumin prior to sequential allergen inhalation challenges. Treatment with the fixed oil reduced the severity of bronchial reactions following allergen challenge; the reactions were less severe in the animals challenged 80 minutes after treatment (86% reduction) than in those challenged after 10 minutes (33% reduction) (*39*).

Effects on cholesterol and triglyceride levels

Administration of the fixed oil to rabbits (15% of a high-cholesterol diet) for 6 weeks reduced total serum cholesterol and triglyceride levels, and increased high-density lipoprotein levels (*40*). A decrease in cholesterol and triglyceride levels in plasma and liver was observed in rats fed a diet containing the fixed oil (10% of a high-cholesterol diet) for 5 weeks (*41*). The fixed oil also increased the levels of high-density lipoprotein, IgG and leukocytes in the serum of mice fed a regular diet containing 10% fixed oil for 6 weeks (*42*). Levels of total serum

cholesterol and very-low-density lipoprotein were consistently lower in rats fed a high-cholesterol diet supplemented with 10% fixed oil for 13 weeks, after having been fed a regular diet for 8 weeks (since birth) (*43*).

Inhibition of platelet aggregation

Administration of the fixed oil to rats (5 ml/kg body weight) inhibited adenosine diphosphate-induced platelet aggregation ex vivo (*14*). However, in another study no effect on adenosine diphosphate-induced platelet aggregation ex vivo was observed in rats fed a diet containing the fixed oil (10% of diet) (*41*). Administration of the fixed oil to rabbits (15% of a high-cholesterol diet) reduced platelet hyperaggregation ex vivo (*40*).

Antihypertensive activity

Rats fed a diet containing 11% fixed oil for 7 weeks showed a decrease in the spontaneous development of hypertension (*41*, *44*). However, the vascular response to the vasoconstrictor hormones norepinephrine, angiotensin II or the calcium channel blocker verapamil remained unchanged (*44*). In another study, however, intragastric administration of the fixed oil to rats (1 ml daily for 3 months) significantly reduced the vascular response to renin and angiotensin II ($P < 0.05$), and significantly increased the formation of vascular prostacyclin-like activity ($P < 0.05$), compared with control rats which received olive oil (*14*). Intragastric administration of the fixed oil to rats enhanced the hypotensive effects of dihydralazine, clonidine and captopril (*45*).

Administration of the fixed oil (147 nmol/hour via an osmotic pump for 8 weeks) to male rats fed a fat-free diet attenuated the cardiovascular responses (increased heart rate and blood pressure) to chronic isolation stress (*46*). Administration of γ-linolenic acid (0.4 mg/kg body weight/hour, via an osmotic pump for 8 weeks) also attenuated the cardiovascular responses to chronic isolation stress in male rats genetically predisposed to hypertension (*47*). Administration of the fixed oil to rats (9% of diet) decreased cardiac arrhythmias induced by ischaemia (*48*).

Antiulcer activity

Intragastric administration of the fixed oil to rats (10 ml/kg body weight) inhibited gastric mucosal damage resulting from ulcers induced by pylorus ligation, non-steroidal anti-inflammatory drugs, and hypothermic restraint. The same dose of the fixed oil also protected gastric mucosa from damage by necrotizing agents (0.6 mol/l hydrochloric acid, 0.2 mol/l sodium hydroxide and 80% ethanol) (*49*).

Antiarthritic activity

Subcutaneous administration of the fixed oil to rats (4 mg/kg body weight) suppressed adjuvant-induced arthritis when administered 1–15 days after adjuvant injection (*50*). Intragastric administration of the fixed oil (0.2 ml/kg body

weight) stimulated phagocytosis, T-lymphocyte production and natural killer cell activity in cyclophosphamide-induced immune suppression in mice (*51*). Daily topical application of the fixed oil (10%) to the skin of pigs for 6 weeks enhanced cell proliferation (*52*).

Nerve function

Administration of the fixed oil (10% of diet) to rats with streptozocin-induced diabetes corrected a decrease in nerve conduction velocity, but did not reduce the prolonged hypoxic time to conduction failure after 1 month of treatment. Capillary density of the endoneurium also increased. Treatment of the animals with flurbiprofen, a cyclooxygenase inhibitor, reduced the effect of the fixed oil (*53*). Intragastric administration of the fixed oil (1 g/kg body weight) for 6 weeks to rats with streptozocin-induced diabetes improved conduction velocity in the sciatic motor nerve and increased sciatic endoneural blood flow (*54*). In another study, administration of the fixed oil (5% of diet) to rats with streptozocin-induced diabetes prevented the decrease in nerve conduction velocity without affecting the levels of nerve sorbitol, fructose and myo-inositol, or the decrease in axonal transport of substance P (*55*).

Anti-embryotoxic activity

Intragastric administration of the fixed oil (0.6 ml daily) to pregnant rats on days 4–8 of gestation significantly reduced the embryotoxic effects of ethanol (*56*).

Clinical pharmacology

Atopic eczema

A meta-analysis of nine placebo-controlled clinical trials (four parallel studies and five with crossover design) of Oleum Oenotherae Biennis in the symptomatic treatment of 311 patients with atopic eczema concluded that the fixed oil was more effective than placebo (*20*). However, two double-blind, placebo-controlled studies that were not included in the meta-analysis, one crossover trial of 123 patients (2–4 g for children, 6–8 g for adults, daily for 4 weeks) (*57*), and one parallel trial of 102 patients (dosage not stated) (*58*), reported negative results. In another double-blind, placebo-controlled study, the efficacy of the fixed oil in the treatment of 39 patients with chronic dermatitis of the hands was assessed. Patients received 6 g fixed oil or placebo daily for 16 weeks. Improvements were observed in both groups, but there was no significant difference between the two groups (*59*). A randomized double-blind, placebo-controlled crossover trial of 99 patients assessed the efficacy of oral administration of the fixed oil for symptomatic treatment of atopic eczema. Patients treated with 2–4 g fixed oil daily for 12 weeks showed a 30–45% improvement in the overall severity of the eczema, including a significant decrease in itching and scaling ($P < 0.002$), as compared with those that received the placebo (*21*). Similar results were reported in a multicentre study (*60*). In a double-blind,

parallel trial, oral administration of 430 mg oil daily to 37 patients with psoriasis resulted in no significant improvement in symptoms (*37*).

A double-blind, placebo-controlled study tested two doses of the fixed oil in the treatment of 51 children with atopic dermatitis. Patients were treated for 8 weeks with either a placebo, the fixed oil, or a combination of 50% placebo and 50% fixed oil (daily dose of 0.5 g/kg body weight, for all treatments). A significant improvement in the overall severity of the clinical symptoms was observed in patients treated with the fixed oil alone ($P = 0.046$). This treatment also increased the concentration of omega-6 fatty acids in the erythrocyte cell membranes (*17*). In a study without controls, oral administration of the fixed oil (3 g) to 12 children daily for 4–20 weeks improved the symptoms of atopic eczema (*2*, *16*, *18*). In a double-blind, placebo-controlled, parallel trial, 58 children with atopic dermatitis were treated daily with either placebo or the fixed oil (2–4 g) for 16 weeks. Plasma concentrations of essential fatty acids increased in the group treated with the fixed oil. Symptomatic improvements occurred in both groups, but there was no significant difference between the two treatments (*61*). The major difficulty with this study was the use of a placebo containing sunflower oil, which has a similar spectrum of essential fatty acids to the fixed oil.

Pharmacokinetics

The serum concentration of eight fatty acids over time was measured after oral administration of the fixed oil to six healthy volunteers. Six capsules of the fixed oil (500 mg each) were administered in both the morning and evening. The fatty acid concentrations in the serum were determined after each administration of the fixed oil as their methyl esters by gas chromatography–mass spectrometry. After administration of the fixed oil, γ-linolenic acid showed an absorption–elimination pattern, and its area under the curve at 24 hours and maximum concentration (C_{max}) were significantly increased over baseline values. The half-life of γ-linolenic acid was shorter after the evening dose (2.7 hours) than after the morning treatment (4.4 hours). Serum levels of dihomo-γ-linolenic acid and arachidonic acid did not increase after administration of the fixed oil (*62*).

Rheumatoid arthritis

Four clinical trials have assessed the efficacy of the fixed oil for the treatment of rheumatoid arthritis in small numbers of patients (*27*–*30*). Three of the trials were unable to establish a significant benefit of using the fixed oil (*27*, *28*).

A 12-week prospective trial involving 20 patients with rheumatoid arthritis assessed the effects of the fixed oil (4.8 ml, equivalent to 360 mg γ-linolenic acid, daily). Prior to the study, all patients discontinued their pharmacological treatments (at least 4 weeks before the start) and non-steroidal anti-inflammatory drugs (4 days before the start). In addition to the fixed oil, patients received vitamin E daily and a product containing zinc, ascorbic acid, niacin and pyridoxine. The symptoms of rheumatoid arthritis, such as joint tenderness, swollen joints, morning stiffness and pain, were assessed at the beginning of the

trial and at 2-week intervals during treatment. Although three patients reported improvements in symptoms during treatment, the study concluded that there was no significant impact on the symptoms of rheumatoid arthritis (*27*). Another 12-week prospective study involving 20 patients with rheumatoid arthritis assessed the efficacy of 20 ml fixed oil daily (equivalent to 750 mg γ-linolenic acid daily) (*28*). The placebo group received olive oil (20 ml daily). All patients discontinued anti-inflammatory medications 7–10 days prior to the study. Although the plasma concentrations of prostaglandin E_2 decreased in four of the patients treated with the fixed oil, no statistically significant changes in symptoms were observed in either group (*27*). The third study was a 6-month, prospective, double-blind, placebo-controlled clinical trial involving 40 patients with rheumatoid arthritis and upper gastrointestinal lesions associated with the use of non-steroidal anti-inflammatory drugs. Nineteen patients received 6 g fixed oil and 120 mg vitamin E daily, while 21 patients in the placebo group received olive oil (6 g daily). Although all patients continued to take non-steroidal anti-inflammatory drugs, three in each group reduced their dosage by one tablet per day. The results of this trial showed a significant reduction in morning stiffness in patients receiving the fixed oil after 3 months of therapy, which was also seen after 6 months of treatment. A significant reduction ($P = 0.04$) in pain and articular index was seen only in patients treated with olive oil (*29*).

A significant benefit of the fixed oil was seen in a double-blind, placebo-controlled study which assessed the efficacy of the fixed oil, alone or in combination with fish oil, for the treatment of rheumatoid arthritis in 34 patients taking non-steroidal anti-inflammatory drugs. Following 12 months of treatment, a significant subjective improvement was observed in patients receiving either the fixed oil (540 mg daily) or the fixed oil and fish oil (450 mg and 240 mg daily, respectively), as compared with the placebo group. In addition, these patients had markedly reduced their intake of non-steroidal anti-inflammatory drugs (*30*).

Premenstrual syndrome

A review of four clinical studies (three with crossover design) reported improvements in the symptoms of premenstrual syndrome (PMS) following treatment with the fixed oil (*31*–*33*). One of these, a double-blind, placebo-controlled crossover study, assessed the efficacy of the fixed oil in women with PMS. After 8 weeks, improvements were seen in all the major clinical symptoms of PMS in both groups. Symptoms improved by 60% in patients treated with the fixed oil and by 40% in the placebo group. Irritability and depression were notably improved in the group treated with the fixed oil (*31*). In a study without controls, 196 women with PMS received two capsules of the fixed oil (500 mg each) twice daily during the luteal phase of the menstrual cycle. The women scored their symptoms during the cycle before treatment and for two cycles after treatment. During the two cycles after treatment, irritability decreased by 77%, depression by 74%, breast tenderness and pain by 76%, headache by 71% and ankle swelling by 63%. These improvements were highly significant ($P < 0.001$)

(*31*). Another study without controls assessed the efficacy of the fixed oil in 68 women with severe PMS, who had failed to respond to at least one other therapeutic regime. Patients were treated with a graduated dosage of the fixed oil, starting with two 500 mg capsules twice daily in the luteal phase only, going up to four capsules twice daily during the whole cycle if there was no response to treatment. Total remission of symptoms was seen in 61% of patients; 23% had partial remission. Of the 36 women who had also experienced breast pain as part of PMS, 26 had total relief from breast pain, five had partial relief and five showed no improvement (*33*).

More recent reviews (*63*, *64*) have assessed the clinical trials: seven placebo-controlled trials were identified, only five of which were randomized. Five of the seven trials (three of which were randomized) reported improvements in the symptoms of PMS. However, two of the best-performed studies, both randomized, double-blind, placebo-controlled crossover studies, failed to show any beneficial effects of the fixed oil (*34*, *35*). In one study, 27 women with PMS received 12 capsules of the fixed oil (500 mg each) or placebo daily. Treatment with the fixed oil did not reduce either the magnitude or the cyclicity of symptoms (*34*). The other study of 38 women with PMS found no difference between the fixed oil (6 g daily for six cycles) and placebo in alleviating symptoms (*35*).

In a study without controls of 19 women with PMS, patients were treated with four capsules of the fixed oil (500 mg each) twice daily for five cycles. A reduction in the scores of individual symptoms (irritability, swollen abdomen, breast discomfort, depression, anxiety, fatigue and general oedema) and total PMS scores was observed after one cycle, and improvements continued over all five cycles (*65*). The clinical and biochemical effects of the fixed oil were investigated in 30 women with severe, incapacitating PMS. The patients were treated with 3 g fixed oil or placebo daily, beginning on day 15 of the cycle until the next menstrual period. Treatment with the fixed oil alleviated PMS symptoms, as compared with treatment with the placebo. No changes were found in the plasma levels of 6-keto-prostaglandin $F_{1\alpha}$, follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, estradiol or testosterone (*66*).

Mastalgia

The effect of the fixed oil on mastalgia, one of the symptoms of PMS, was assessed in a randomized, double-blind, placebo-controlled crossover study. Seventy-three women were treated with the fixed oil or placebo for 3 months. In patients with both cyclical and non-cyclical mastalgia, treatment with the fixed oil significantly reduced breast pain and tenderness ($P < 0.02$–0.05) (*25*). Another double-blind, placebo-controlled clinical trial assessed the efficacy of the fixed oil in 42 women with cyclic breast pain and tenderness. Patients were treated with eight capsules (500 mg each) daily for 12 weeks. The fixed oil was significantly more effective than placebo in reducing nodularity, breast tenderness and irritability, as well as promoting a feeling of well-being ($P < 0.05$) (*67*).

A review of the randomized trials and studies without controls involving 291 women with severe persistent mastalgia was performed. Patients were treated with either the fixed oil (six capsules of 500 mg), bromocriptine (5 mg) or danazol (200 mg) daily for 3–6 months. In patients with cyclical mastalgia, good responses were obtained in 45% of patients treated with the fixed oil, in 47% treated with bromocriptine and in 70% treated with danazol. The response rate in patients with non-cyclical mastalgia was 27%, 20% and 31%, respectively. Adverse reactions were reported in 2% of patients treated with the fixed oil, in 33% of patients treated with bromocriptine and in 22% of those treated with danazol (*26*). A review of 17 years of drug treatment at a mastalgia clinic described the efficacy of daily administration of danazol (200 mg), bromocriptine (5 mg) and the fixed oil (six capsules of 500 mg) in 414 patients (324 with cyclical and 90 with non-cyclical mastalgia). Treatment with danazol was most effective (in 79% of patients); the fixed oil and bromocriptine were effective in 58% and 54% of patients, respectively. However, the rates of adverse reactions were higher in patients treated with danazol and bromocriptine (30% and 35%, respectively) than in those treated with the fixed oil (4%) (*24*).

Diabetic neuropathy

Dietary supplementation with the fixed oil was associated with a clinical, neurophysiological and quantitative sensory improvement in 22 male and female patients with diabetic polyneuropathy (*22*). After a preliminary trial in 22 patients with diabetes, positive effects were also reported in many neurological and neurophysiological parameters in a parallel double-blind study of 111 male and female patients with mild diabetic neuropathy (*23*).

Oral administration of the fixed oil to male patients with diabetes and healthy male volunteers (20 g, enriched with vitamin E) daily for 1 week enhanced erythropoiesis and changed the serum fatty acid profiles in both groups. Inhibition of platelet-activating factor 4 and plasma β-thromboglobulin was also observed in both groups (*68*).

Menopausal flushing

The efficacy of the fixed oil was evaluated in a randomized, double-blind, placebo-controlled study of 35 women with hot flushes. The women were treated with either four capsules of the fixed oil (500 mg each, supplemented with 10 mg natural vitamin E) or placebo twice daily for 6 months. No significant improvement in menopausal flushing was observed in women treated with the oil, as compared with the placebo (*36*).

Uraemic skin disorders

The effects of oral administration of the fixed oil on plasma fatty acid concentrations and the symptoms of uraemic skin disorders (dryness, pruritus and erythema) were evaluated in a double-blind study of haemodialysis patients.

Patients treated with the fixed oil (2 g daily) for 6 weeks showed a significant increase in plasma dihomo-γ-linolenic acid ($P < 0.05$) and a significant decrease in uraemic pruritus ($P < 0.05$) (*69*).

Contraindications

No information available.

Warnings

Oleum Oenotherae Biennis may precipitate symptoms of undiagnosed temporal lobe epilepsy, particularly in schizophrenic patients or patients taking epileptogenic drugs such as phenothiazines (*70–72*).

Precautions

General

Oleum Oenotherae Biennis should be used with caution in patients with a history of epilepsy, particularly those with schizophrenia, or those taking epileptogenic drugs such as phenothiazines (*19*, *70*).

Drug interactions

Oleum Oenotherae Biennis inhibited platelet aggregation in animals (*14*, *40*) and inhibited platelet-activating factor in humans (*68*). Therefore, patients taking anticoagulant drugs in conjunction with the fixed oil should be closely monitored.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Oleum Oenotherae Biennis should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Headaches, nausea, loose stools and diarrhoea following treatment with Oleum Oenotherae Biennis have been reported (*2*). Administration of the fixed oil precipitated symptoms of undiagnosed temporal lobe epilepsy in schizophrenic patients taking epileptogenic drugs, in particular phenothiazines (*72*).

Dosage forms

Fixed oil, neat or in capsule form (*1*, *13*). Store in a well-filled, airtight glass container, protected from heat and light.

Posology

(Unless otherwise indicated)
Daily dosage: 320–480 mg fixed oil (calculated as γ-linolenic acid) in divided doses for atopic eczema, and 240–320 mg in divided doses for mastalgia (*19*).

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Rhizoma Piperis Methystici

Definition

Rhizoma Piperis Methystici consists of the dried rhizomes of *Piper methysticum* G. Forst. (Piperaceae) (*1–3*).

Synonyms

Macropiper latifolium Miq., *M. methystiscum* (G. Forst.) Hook. et Arnott, *Piper inebrians* Soland (*3*).

Selected vernacular names

Ava, ava root, awa, gea, gi, kao, kava, kavakava, kava-kava, kava-kava root, kavapipar, kawa, kawa kawa, kawa pepper, Kawapfeffer, malohu, maluk, maori kava, meruk, milik, racine de poivre enivrant, Rauschpfeffer, rhizoma de kava-kava, rhizoma di kava-kava, yagona, yaqona (*3–5*).

Geographical distribution

Indigenous to and cultivated in the islands of Oceania, from Hawaii to Papua New Guinea, with the notable exception of New Caledonia, New Zealand and most of the Solomon Islands (*5*).

Description

A perennial shrub up to 7 m high, robust and fairly succulent. Leaves cordate, pointed, smooth and green on both sides, up to 25 cm long. Root can reach 60 cm in length and 8 cm in diameter; may eventually become a heavy knotted mass, 8–25 cm wide. Petioles up to 6 cm long; flowers in irregular spadices with lateral root up to 3 m long (*5*).

Plant material of interest: dried rhizome

General appearance

Irregular, transverse and longitudinal pieces, varying considerably in size and shape: 3–20 cm long and 1–5 cm in diameter. Outer surface light yellowish or greyish-brown, longitudinally wrinkled, with large whitish circular root scars.

Fracture coarsely fibrous, inner surface yellow-white; bark thin; xylem distinctly radiate; pith large (*1*, *2*, *6*, *7*).

Organoleptic properties

Odour: slight, agreeable; taste: sweetish, pungent, sometimes slightly bitter, followed by slight numbness (*1*, *2*, *7*).

Microscopic characteristics

Transverse section through the xylem shows small channels with vascular bundles; cross section through the xylem shows narrow vessels, which are located around the pith and alternate with large pith rays. Additional vessels across the pith; xylem has tracheid-like elements; phloem has fewer and thinner-walled cells. Secretory canals contain a fine, brown resinous mass. Unpeeled rhizome has a narrow cork-layer. Primary bark contains rays of collenchyma, tissues, numerous resin and storage cells around the phloem (*1*–*3*).

Powdered plant material

Light yellow-brown. Contains large oval pith cells. Secretion canals containing yellow to red-brown masses of resin; elongated cells of the medullary rays porous and slightly lignified. Vessels lignified and reticulate; fibres slightly lignified, large lumen and occasionally branched oval ends. Xylem parenchyma, cells lignified and slightly elongated. Numerous simple or 2–3 compound starch grains, the individual grains being spheroidal or planoconvex, 10–30 µm and sometimes up to 45 µm in diameter, many showing radial or triangular central clefts. Calcium oxalate crystals absent (*1*, *2*, *7*).

General identity tests

Macroscopic, microscopic and microchemical examinations (*1*, *2*, *7*), and thin-layer chromatography for the presence of characteristic unsaturated α-pyrones known as kava pyrones (*1*, *2*, *8*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

Foreign organic matter

Not more than 2% (*1*, *2*).

Total ash

Not more than 8% (*1*, *2*).

Acid-insoluble ash

Not more than 1.5% (*1*).

Water-soluble extractive

Not less than 5% (*1*).

Loss on drying

Not more than 12% (*2*, *3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

Other purity tests

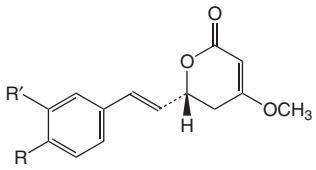
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 3.5% kava pyrones, as determined by infrared absorption spectroscopy at $1705 \pm 5\,cm^{-1}$ (*2*). Complete qualitative analytical profiles can be obtained by high-performance liquid chromatography–electrospray mass spectrometry (*12*). A high-performance liquid chromatography method is also available for quantitative analysis (*3*).

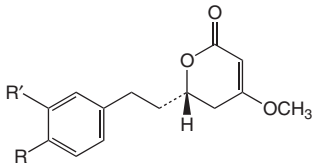
Major chemical constituents

The major constituents are kava lactones (also known as kava pyrones) with the major lactones being kawain (1.8%), methysticin (1.2%), dihydromethysticin (0.5%), demethoxyyangonin (1.0%), yangonin (1.0%) and dihydrokawain (1.0%). At least 13 other lactones, two chalcones and a number of free aromatic acids are known (*3–5*, *13*). The structures of the representative lactones are presented below.



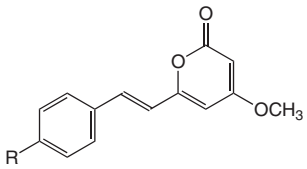
kawain R = R′ = H

methysticin R, R′ = O-CH_2-O



dihydrokawain R = R′ = H

dihydromethysticin R, R′ = O-CH_2-O



yangonin R = OCH_3

demethoxyyangonin R = H

Medicinal uses

Uses supported by clinical data

Short-term symptomatic treatment of mild states of anxiety or insomnia, due to nervousness, stress or tension (*14–24*).

Uses described in pharmacopoeias and in traditional systems of medicine

To induce relaxation, reduce weight and treat fungal infections (*5*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, common cold, cystitis, gonorrhoea, headaches, menstrual irregularities, urinary infections and warts (*4*, *5*).

Pharmacology

Experimental pharmacology

Behavioural effects

Intraperitoneal administration of an aqueous extract of Rhizoma Piperis Methystici (62.5 mg/kg body weight) decreased the spontaneous activity of mice. This effect lasted for 2 hours without loss of muscle tone (*25*). The same extract, however, was not active in mice or rats when administered orally in single doses of 0.5–2.5 g/kg body weight. A dichloromethane extract of the rhizome (150 mg/kg body weight, administered intraperitoneally) decreased spontaneous motility by 46%, and markedly reduced motor control (by 50%)

in mice (*25*, *26*). At this dose, the extract also induced hypnosis and analgesia (*25*). Intraperitoneal administration of aqueous, dichloromethane and lyophilized aqueous extracts of the rhizome (62.5–250 mg/kg body weight) reduced spontaneous activity in mice and rats (*27*, *28*). Intraperitoneal administration of an aqueous or dichloromethane extract of the rhizome (120 mg/kg body weight) suppressed apomorphine-induced hyperactivity in rats (*25*). Intraperitoneal administration of a lipid-soluble fraction of an aqueous rhizome extract (doses up to 300 mg/kg body weight) decreased the conditioned avoidance response in rats. An aqueous extract, however, was inactive at doses up to 500 mg/kg body weight (*27*). Intraperitoneal administration of an extract of the rhizome (equivalent to 50–100 mg kava pyrones/kg body weight) or (±)-kawain, a synthetic kava lactone (10–50 mg/kg body weight), reduced muscle tone in cats (*29*).

Analgesic activity

Intraperitoneal administration of a dichloromethane extract of the rhizome (150 mg/kg body weight) produced analgesia in mice (*25*). Intraperitoneal or intragastric administration of an aqueous or lipid extract of the rhizome (150–250 mg/kg body weight) produced analgesia in mice, as measured by tail-flick reaction times and suppression of acetic acid-induced writhing (*30*). Both dihydrokawain and dihydromethysticin exhibited analgesic effects when administered intraperitoneally to rats (140 mg/kg body weight), as determined by an increase in tail-flick reaction times (*31*).

Neurological effects

Depression of the central nervous system was observed in rodents after intraperitoneal administration of an aqueous rhizome extract (50–170 mg/kg body weight) (*32*). Intraperitoneal administration of an aqueous extract (300 mg/kg body weight) or a chloroform extract (140 mg/kg body weight) of the rhizome depressed the central nervous system and potentiated the effects of barbiturates in mice. Administration of dihydromethysticin to mice potentiated pentobarbital-induced sleeping time by 400%, while dihydrokawain, yangonin and kawain were only moderately active (150–235%) (*33*). A dichloromethane extract of the rhizome administered intraperitoneally to mice (150 mg/kg body weight) induced hypnosis (*25*). The hypnotic and sedative effects of a dichloromethane rhizome extract (300 mg/kg body weight, administered intraperitoneally) were significantly prolonged in mice by the concurrent administration of ethanol (2 g/kg body weight; $P < 0.001$) (*30*). A saline extract of the rhizome had an effect on crayfish abdominal ganglia in vitro (0.05 g/ml) (*34*). Intraperitoneal administration of an extract of the rhizome (equivalent to 50–100 mg kava pyrones/kg body weight) to cats had a significant effect on EEG recordings, inducing high-amplitude delta waves, spindle-like formation, and continuous alpha- or beta-synchronization in amygdala recordings ($P < 0.001$). Hippocampal responses, following stimulation of the

amygdala nucleus, increased significantly in amplitude in cats treated intraperitoneally with the rhizome extract (equivalent to 100 mg kava pyrones/kg body weight; $P < 0.01$) or (±)-kawain (50 mg/kg body weight; $P < 0.05$) (*29*).

The neuroprotective effects of an acetone extract of the rhizome and kava pyrones have been demonstrated both in vivo and in vitro. A standardized acetone extract of the rhizome, methysticin and dihydromethysticin protected rodents against hypoxia or ischaemia-induced cerebral damage (*35*). The standardized extract also protected against neuronal damage in cultured neurons from chick embryo cerebral hemispheres (*36*).

Although the neuroprotective mechanisms of the rhizome are not well understood, recent investigations have indicated that kava pyrones may exert their effects by activating several neurotransmitter systems, such as the adrenergic (*37*), mesolimbic dopaminergic (*38*), gabaminergic (*39*), glutamatergic (*40*, *41*), and serotonergic receptor systems (*42*, *43*). An extract of the rhizome containing 58% kava pyrones enhanced the binding of [^{3}H]muscimol to γ-aminobutyric acid-A receptors in a concentration-dependent manner in rat hippocampus, amygdala and medulla oblongata in vitro (ED_{50} 200–300 µmol/l) (*39*). However, another study found no significant interaction in vitro or in vivo of a dichloromethane rhizome extract or kava pyrones with γ-aminobutyric acid (A and B) or benzodiazepine receptor binding sites (*44*). Both kawain and dihydromethysticin (10–100 µmol/l) reduced the field potential changes induced by the serotonin-1A agonist, ipsapirone, in the CA1 and CA3 areas of guinea-pig hippocampal slices in vitro. These results suggest that both compounds may modulate serotonin-1A receptor activity (*43*). Methysticin and kawain inhibited the uptake of ^{3}H-labelled norepinephrine, but not of ^{3}H-labelled serotonin, in synaptosomes prepared from the cerebral cortex and hippocampus of rats (*37*). Intragastric administration of (+)-dihydromethysticin in a single dose (100 mg/kg body weight), or chronic intragastric administration of (±)-kawain (10.8 mg/kg body weight) daily for 78 days to rats did not alter dopamine or serotonin levels in the striatal or cortical brain regions (*45*).

Anticonvulsant activity

Intraperitoneal administration of an aqueous extract (300 mg/kg body weight) or a chloroform extract (140 mg/kg body weight) of the rhizome to mice inhibited strychnine-induced convulsions (*33*). The anticonvulsant activity of methysticin and other kava pyrones against electroshock- and chemically-induced seizures has been demonstrated in mice and rats (*46–48*). Intraperitoneal administration of dihydromethysticin and dihydrokawain inhibited electroshock-induced seizures at doses of 25 and 60 mg/kg body weight, respectively, in mice and rats (*47*). Methysticin (10–100 µmol/l) was also active in different in vitro models of seizure-like events using extracellular recordings in rat temporal cortex slices containing the hippocampus and entorhinal cortex. Methysticin suppressed epileptiform activity independent of the stimulus (low calcium or magnesium, or high potassium perfusion medium), suggesting a

direct effect of the compound on neuron membranes, thus inhibiting neuron excitability (*40*). Other studies have demonstrated that (+)-kawain and (±)-kawain inhibited voltage-dependent calcium and sodium channels of rat cerebrocortical synaptosomes (*41, 49, 50*). In these synaptosomes, it was also shown that (±)-kawain inhibited the increase in intracellular calcium and glutamate release induced by veratridine and potassium chloride (*49*). Both (±)-kawain and methysticin inhibited voltage-dependent sodium channels in rat CA1 hippocampal neurons in vitro (1–400 µmol/l) (*51*).

Antispasmodic activity

An aqueous rhizome extract, kawain, dihydrokawain, methysticin and dihydromethysticin inhibited serotonin and nicotine-induced contractions of guinea-pig ileum in vitro (*52, 53*). The antispasmodic effects were attributed to a direct musculotropic action. Dihydromethysticin also inhibited contractions of rat colon and uterus in vitro induced by serotonin, acetylcholine and barium (*53*). Desmethoxyyangonin, dihydromethysticin and kawain inhibited serotonin-induced contractions of rat uterus in vitro at concentrations of 3.2, 7.5 and 10.0 µg/ml, respectively (*54*). Aqueous, dichloromethane and lyophilized extracts of the rhizome induced relaxation of rat uterus in vitro (ED_{50} 22.5 µg/ml) (*28*). The effects of an aqueous extract of the rhizome on muscle contractility and neuromuscular transmission were investigated in mouse hemidiaphragms and frog sartorius muscles in vitro using twitch tension and intracellular recording techniques. The extract (2–5 mg/ml) induced muscle relaxation by direct action on muscle contractility rather than by inhibition of neuromuscular transmission (*55*).

Antimicrobial activity

A hydroalcoholic extract of the rhizome inhibited the growth in vitro of *Aspergillus fumigatus, A. niger, Penicillium digitatum, Rhizopus nigricans, Trichophyton mentagrophytes, Candida albicans* and *Saccharomyces pastorianus* (*56*). However, an aqueous extract of the rhizome did not inhibit the growth in vitro of *Trichophyton rubrum, Microsporum canis* or *Epidermophyton floccosum* (*57*).

Clinical pharmacology

Anxiety

At least seven double-blind, controlled clinical studies have assessed the efficacy of two extracts of Rhizoma Piperis Methystici for symptomatic treatment of anxiety (*17, 18, 21–24, 58*). Two of these studies were performed with a hydroalcoholic extract standardized to contain 15% kava pyrones (*22, 58*), while the other studies used an extract standardized to contain 70% kava pyrones (*17, 18, 21, 23, 24*).

Two placebo-controlled trials investigated the effect of both standardized extracts in women with climacteric psychosomatic disturbances. In the first study, 40 such women were treated with either a placebo or 200–400 mg extract

(30–60 mg kava pyrones) daily for 8–12 weeks. Using the Kuppermann Index and Anxiety Status Index, the extract was found to be superior to the placebo (*22*). In the second study, a further 40 such women were treated with 300 mg extract (210 mg kava pyrones) daily for 8 weeks in a randomized, placebo-controlled, double-blind study. The outcome was assessed using the Hamilton Anxiety Rating Scale; the Depression Status Inventory and the Kuppermann Index were also used. The total score on the Hamilton Anxiety Rating Scale decreased after 1 week of treatment with the extract, and reached a plateau at 4 weeks. The therapeutic response to the extract was significant, as compared with the response to the placebo ($P < 0.001$) (*23*). After 8 weeks of treatment with the extract, the mean score on the Hamilton Anxiety Rating Scale decreased from 31.1 to 5.5. In the group which received the placebo, the mean score decreased from 30.15 to 22.50. The mean score on the Depression Status Inventory decreased significantly from 42.5 to 24.8 ($P < 0.01$). The mean score on the Kuppermann Index also decreased significantly from 20.35 to 3.60 ($P < 0.01$) (*23*).

A double-blind, placebo-controlled study of 58 patients with symptoms of anxiety, tension or agitation of non-psychotic origin assessed the effectiveness of the extract containing 70% kava pyrones (equivalent to 210 mg kava pyrones) daily for 4 weeks. The outcome was assessed using the total score on the Hamilton Anxiety Rating Scale, and other rating scales (the Erlanger Scale for Anxiety, Clinical Global Impressions and the Fischer Somatic Symptoms). After 1 week, patients treated with the extract showed a reduction in the total score on the Hamilton Anxiety Rating Scale as compared with the placebo group. The difference between the scores of the two groups increased after 4 weeks of treatment (*17*).

A randomized double-blind comparative study assessed the efficacy of the extract containing 70% kava pyrones in 172 patients with symptoms of anxiety, tension and agitation of non-psychotic origin. Patients received either 300 mg extract (210 mg kava pyrones), 15 mg oxazepam or 9 mg bromazepam daily for 6 weeks. The main criterion for assessment was the total score on the Hamilton Anxiety Rating Scale. No significant difference was observed between the treatments (*24*). In another randomized study which involved several centres, the efficacy of the extract containing 70% kava pyrones was tested in 100 patients with anxiety of non-psychotic origin (as defined in the *Diagnostic and statistical manual of mental disorders*, 3rd ed. (*59*)). Patients were treated with either a placebo or 300 mg extract (equivalent to 210 mg kava pyrones) daily for 24 weeks and the outcome was assessed using the Hamilton Anxiety Rating Scale. Adjunct rating scales were the Clinical Global Impressions and Von Zerssen mood scale. In patients treated with the extract, the decrease in the Hamilton Anxiety Rating Scale (mean scores of 30.7 and 9.7 at weeks 0 and 24, respectively) was significant as compared with the placebo group ($P < 0.005$). The scores on the Clinical Global Impressions and Von Zerssen mood scale also improved after 24 weeks of treatment with the extract (*21*). A randomized study of 58 patients also assessed the efficacy of the extract containing 70% kava pyrones for the treatment of anxiety of non-psychotic origin. Patients were treated with either a

placebo or 300 mg extract (equivalent to 210 mg kava pyrones) daily for 4 weeks and therapeutic efficacy was assessed using the Hamilton Anxiety Rating Scale. After 1 week, there was a significant reduction in the scores (mean scores of 25.6 and 16.2 at weeks 0 and 1, respectively) in the treated group as compared with the placebo group ($P = 0.004$) (*18*).

A randomized, double-blind pilot study investigated the effects of the extract containing 15% kava pyrones in 59 patients with pre-operative anxiety (*58*). Although improvements in mood were observed using a psychostatus score, only two doses of the extract (equivalent to 60 mg kava pyrones daily) were administered, and thus the clinical significance of this study is questionable.

An additional nine double-blind studies have been performed with (±)-kawain (*60*, *61*). Two of the studies were comparative studies and seven were placebo-controlled. Therapeutic anxiolytic activity was achieved with doses of 200–600 mg (±)-kawain daily (*60*). Kawain is available in Germany and Switzerland as an over-the-counter medication.

Insomnia

Two single-blind and four double-blind, placebo-controlled clinical trials investigated the effect of a rhizome extract standardized to contain 70% kava pyrones on EEG recordings, and intellectual and motor functions of healthy volunteers (*14*, *16*, *62–65*). Changes in EEG recordings and psychomotor test results showed no evidence of a decrease in vigilance or responsiveness in volunteers treated with 600 mg extract (equivalent to 420 mg kava pyrones) daily for 5 days (*64*, *65*). Examination of EEG recordings during sleep of healthy volunteers given a single dose of 300 mg extract (equivalent to 210 mg kava pyrones) showed an increased sleep spindle density of 20% and an increase in slow-wave sleep (i.e. deep sleep), but the rapid eye movement phase was not suppressed (*14*). Daily doses of 300 or 600 mg extract (equivalent to 210 or 420 mg kava pyrones), respectively, for 1 week increased the beta/alpha index typical for the pharmaco-EEG profile of anxiolytics. The increase in beta activity was most marked in the $beta_2$ range (*16*). In two studies, administration of 300 mg extract (equivalent to 210 mg kava pyrones) daily for either 8 or 14 days, taken with or without ethanol, had no influence on the safety-related performance of healthy volunteers (*62*, *63*).

In a randomized, double-blind crossover study involving 12 healthy volunteers, administration of daily single doses of a rhizome extract standardized to contain 30% kava pyrones (400 mg extract containing 120 mg kava pyrones) was compared with daily single doses of diazepam (10 mg) or a placebo in a 7-day trial. Changes in EEG recordings and psychometric test results showed no evidence of a decrease in vigilance in the group treated with the extract (*66*). Safety-related performance was assessed in another study after administration of an extract standardized to contain 30% kava pyrones, bromazepam or a combination of extract and bromazepam. Safety-related performance remained unaffected in healthy volunteers treated daily with 400 mg extract (equivalent

to 120 mg kava pyrones for 14 days), whereas it was impaired after treatment with bromazepam (9 mg daily) or the extract/bromazepam combination. No differences were observed following treatment with bromazepam or the combination, indicating that the extract did not have an additive effect when given in combination with bromazepam (*67*).

Contraindications

During pregnancy and lactation, and in patients with endogenous depression (*15*) or liver disease.[1]

Warnings

Rhizoma Piperis Methystici should not be taken for more than 3 months without medical advice. Even when administered within the recommended dosage range, motor reflexes and the ability to drive or operate heavy machinery may be adversely affected (*15*).

Precautions

Drug interactions

The effectiveness of centrally acting drugs such as alcohol, barbiturates and other psychopharmacological agents may be potentiated (*15*). One case of possible drug interaction between Rhizoma Piperis Methystici, alprazolam, cimetidine and terazosin has been reported (*69*). The clinical significance of this interaction has not yet been established.

Carcinogenesis, mutagenesis, impairment of fertility

Oral administration of up to 600 mg/kg body weight of a standardized extract containing 70% kava pyrones did not increase the formation of micronucleated polychromatic erythrocytes and did not lead to any change in the ratio of polychromatic to normochromatic erythrocytes. There was no increase in the number of revertants in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with or without metabolic activation, at doses up to 2.5 mg/plate in the *Salmonella*/microsome assay (*3*).

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

See Contraindications.

[1] Several cases of liver toxicity have been reported in Europe following use of herbal products containing extracts of Rhizoma Piperis Methystici (*68*).

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or paediatric use. Therefore, Rhizoma Piperis Methystici should not be administered to children without medical supervision.

Adverse reactions

In a surveillance study involving 4049 patients who received a standardized extract of Rhizoma Piperis Methystici containing 70% kava pyrones (150 mg extract, equivalent to 105 mg kava pyrones) orally daily for 7 weeks, adverse reactions were reported in 61 patients (1.5%). The major reactions were gastrointestinal complaints or allergic skin reactions (3, *20*). In a study of 3029 patients given a standardized extract of the rhizome containing 30% kava pyrones (800 mg extract, equivalent to 240 mg kava pyrones) orally daily for 4 weeks, adverse reactions were reported in 2.3% of patients. Nine cases of allergic reactions, 31 cases of gastrointestinal complaints, 22 cases of headache or dizziness, and 11 cases of other undefined problems were reported (3, *70*). Chronic administration of the rhizome or preparations thereof may cause a transient, yellow discoloration of the skin and nails, which is reversible upon discontinuation of the drug (*15*). Excessive, chronic abuse of infusions of the rhizome has been historically associated with a scaly, eruptive dermopathy of unknown etiology (*71*). Allergic skin reactions and ichthyosis have also been reported (*72–74*). In two patients, a reaction was seen in areas rich in sebaceous glands following 3 weeks of systemic antidepressant therapy with the rhizome. The reaction resulted in the formation of papules and plaques on the face, and ventral and dorsal thorax (*75*). One study in an Australian aboriginal community found that chronic abuse of the rhizome led to malnutrition and weight loss, increased levels of γ-glutamyltransferase, decreased levels of plasma protein, and reduced platelet volume and lymphocyte numbers (*76*). In a healthy volunteer, disturbances of visual accommodation, such as enlargement of the pupils, and disturbances in oculomotor equilibrium, were reported following the ingestion of large doses of kava (*77*). Chronic consumption (6 months) of large quantities of an infusion of the rhizome (5–6 cups daily) has been reported to cause anorexia, diarrhoea and visual disturbances (*73*). A single case report of athetosis involving the limbs, trunk, neck and facial musculature, with marked athetosis of the tongue, was associated with chronic consumption of large quantities of the rhizome (*78*).

There is one report of acute hepatitis in a 39-year-old woman following ingestion of a rhizome preparation (*79*). However, the identity of the material was not authenticated.

Dosage forms

Comminuted crude drug and extracts for oral use (*15*). Store in a tightly closed container, away from light.

Posology

(Unless otherwise indicated)
Daily dosage: crude drug and extracts equivalent to 60–210 mg kava pyrones (*15*, *18*, *21–24*).

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Cortex Pruni Africanae

Definition

Cortex Pruni Africanae consists of the dried bark of the trunk of *Prunus africana* (Hook. f.) Kalkman (Rosaceae).

Synonyms

Pygeum africanum Hook. f. (*1*, *2*).

Selected vernacular names

African plum tree, African prune, armaatet, bitter almond, Bitteramandel, chati, inkhokhokho, inyangazoma-elimnyama, kiburabura, lemalan migambo, mueri, muiru, murugutu, mutimailu, mweria, mwiritsa, nuwehout, ol-koijuk, oromoti, red stinkwood, rooistinhout, tenduet, tendwet, twendet, umdumizulu, umkakase, umkhakhazi, umlalume (*1*, *3*–*9*).

Geographical distribution[1]

Found in mountain forests of equatorial Africa including Angola, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Mozambique, Republic of Congo, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe (*2*, *3*, *8*).

Description

An evergreen tree, usually 10–25 m high, with straight, cylindrical trunk and dense, rounded crown. Leaves alternate, 8–12 cm long, long-stalked, simple, elliptic, bluntly pointed at apex, with shallow crenate margins; leathery, deep green and glossy, with midrib sharply impressed or channelled on upper surface and strongly prominent on underside; smell of almonds when bruised. Leaf-stalks and young branchlets often reddish. Flowers small, white or cream, fragrant, in axillary racemes 3–8 cm long; corolla lobes up to 2 mm long. Fruits cherry-shaped, red to purplish-brown, 8–12 mm in diameter; very bitter flesh and bony stone. Wood pale red, with strong cyanide smell when freshly cut,

[1] Owing to overexploitation and other factors, *Prunus africana* has been listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (*10*).

darkening to rich dark red or mahogany-brown on exposure to air; straight-grained and even textured, strong and elastic, very hard and very heavy (*3*, *8*, *11*).

Plant material of interest: dried trunk bark

General appearance

Red to blackish-brown, deeply square-fissured or corrugated (*1*, *3*, *8*).

Organoleptic properties

Odour: strong, characteristic almond smell (*11*).

Microscopic characteristics

To be established in accordance with national requirements.

Powdered plant material

To be established in accordance with national requirements.

General identity tests

Macroscopic examination (*3*, *8*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

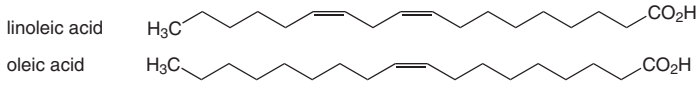
Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

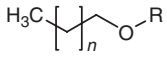
Chemical assays

Qualitative and quantitative analysis for the major constituents, docosanol and β-sitosterol, are performed by gas chromatography–mass spectrometry (*15*, *16*). Quantitative analysis of docosyl (*E*)-ferulate is performed by high-performance liquid chromatography (*17*).

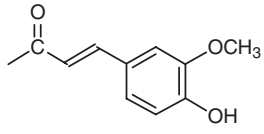
Major chemical constituents

The purported active constituents of a lipophilic extract of Cortex Pruni Africanae include docosanol (0.6%) and β-sitosterol (15.7%). Other major constituents include alkanols (tetracosanol [0.5%] and *trans*-ferulic acid esters of docosanol and tetracosanol), fatty acids (62.3%, comprising myristic, palmitic, linoleic, oleic, stearic, arachidic, behenic and lignoceric acids); sterols (sitosterone [2.0%] and daucosterol) and triterpenes (ursolic acid [2.9%], friedelin [1.4%], 2-α-hydroxyursolic acid [0.5%], epimaslinic acid [0.8%] and maslinic acid) (*2*, *15–21*). The structures of docosanol, tetracosanol, linoleic acid, oleic acid, β-sitosterol, sitosterone, ursolic acid and friedelin are presented below.

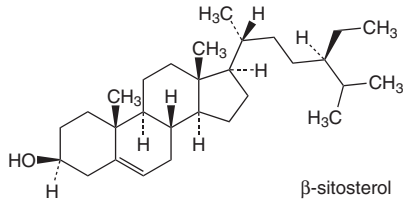


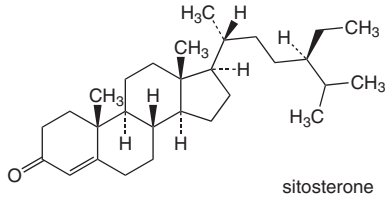


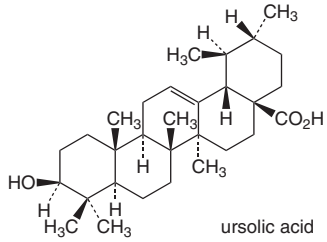
	n	R
docosanol	20	H
tetracosanol	22	H
docosyl (*E*)-ferulate	20	(*E*)-ferulyl
tetracosyl (*E*)-ferulate	22	(*E*)-ferulyl

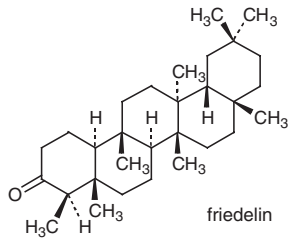


(*E*)- ferulyl









Medicinal uses

Uses supported by clinical data

Treatment of lower urinary tract symptoms of benign prostatic hyperplasia (BPH) stages I and II, as defined by Alken (e.g. nocturia, polyuria and urinary retention), in cases where diagnosis of prostate cancer is negative (*22–34*).

Uses described in pharmacopoeias and traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

As a purgative, for the treatment of stomach and intercostal pain (*3*, *35*).

Pharmacology

Experimental pharmacology

Effects on the prostate

Intraperitoneal administration of a lipophilic trunk bark extract (10 mg/kg body weight) daily for 20 days enhanced the secretory activity of the prostate and seminal vesicles in castrated rats, and antagonized the activity of testosterone on these glands. However, in rats which were castrated and adrenalectomized, the extract potentiated the effects of testosterone on both the prostate and seminal vesicles and also increased the concentration of pituitary gonadotropins

(*36*). Intragastric administration of a lipophilic extract of the trunk bark to rats (2 mg/kg body weight) daily for 20–50 days stimulated the secretory activity of the prostate and prevented the development of prostate hyperplasia induced by intraperitoneal injection of human prostate adenoma tissue (*37*). Intragastric administration of a lipophilic extract of the crude drug to rats (100 mg/kg body weight) daily for 3 days also increased prostate secretions (*38*).

Hormonal activity

Intragastric administration of a lipophilic extract of the trunk bark to ovariectomized mice (150 mg/kg body weight) inhibited estrogen binding (*39*). Intragastric administration of a methylene chloride extract of the trunk bark to male mice inhibited the activity of 5α-reductase (ED_{50} 0.78 mg/ml). The same extract also inhibited the activity of aromatase and 5α-reductase in vitro (IC_{50} 0.98 and 0.78 mg/ml, respectively) (*39*). In another study, however, a lipophilic extract only marginally inhibited the activity of 5α-reductase from human prostate cells in vitro at a concentration of 63 µg/ml (*40*).

Anti-inflammatory activity

Intragastric administration of a lipophilic extract of Cortex Pruni Africanae (400 mg/kg body weight) suppressed carrageenan-induced footpad oedema in rats. Intraperitoneal administration of the extract to rats (100 mg/kg body weight) also reduced the increase in vascular permeability caused by histamine (*41*). A lipophilic extract of the trunk bark inhibited the production of 5-lipoxygenase metabolites, such as chemotactic leukotrienes, in human polymorphonuclear cells stimulated by the calcium ionophore A23187 (*42*, *43*).

Antispasmodic activity

A lipophilic extract of the crude drug administered intragastrically to rats inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol (*44*). A reduction in carbachol-induced spasms of the bladder was observed after intragastric administration of a lipophilic extract of the crude drug to guinea-pigs (*36*). Intragastric administration of a lipophilic extract of the trunk bark to rabbits (100 mg/kg body weight) prevented the development of contractile dysfunction induced by partial obstruction of the bladder (*45*). A lipophilic extract of the crude drug improved the contractility of the detrusor muscle of the bladder in old rats (*46*).

Inhibition of cell proliferation

A chloroform extract of the crude drug (10 µg/ml) significantly inhibited proliferation of Swiss 3T3 mouse fibroblasts induced by basic fibroblast growth factor and epidermal growth factor in vitro ($P < 0.05$) (*47*, *48*). DNA synthesis in rat prostatic fibroblasts, induced by insulin-like growth factor, epidermal growth factor, 12-*O*-tetradecanoyl phorbol-13-acetate or basic fibroblast

growth factor, was inhibited in vitro by a 95% ethanol extract of the trunk bark (IC_{50} 12.4, 12.6, 4.5 and 7.7 µg/ml, respectively) (*49*).

Toxicity

In acute and chronic toxicity studies in mice and rats, no adverse reactions or fatalities were observed after intragastric administration of a single dose of a lipophilic extract of the trunk bark (1–6 g/kg body weight in mice and 1–8 g/kg body weight in rats). No adverse reactions were observed in mice and rats after chronic intragastric administration of the extract (60 and 600 mg/kg body weight, respectively, daily for 11 months) (*2*).

Clinical pharmacology

Benign prostatic hyperplasia

Placebo-controlled clinical trials

Eleven double-blind, placebo-controlled studies assessed the effects of an oral lipophilic extract of Cortex Pruni Africanae in the symptomatic treatment of 717 men with mild to moderate BPH (*22–28*, *30*, *31*, *33*, *34*). The number of patients in each study ranged from 14 to 255, and the dosage of the trunk bark extract was 75–200 mg daily for at least 6 weeks. Eight studies measured maximum urinary flow and 10 studies measured daytime and night-time polyuria (*22–26*, *28*, *30*, *31*, *33*, *34*). One study also included comparison with a combination of the trunk bark extract and medroxyprogesterone acetate (*34*). Seven trials reported a significant improvement in maximum urinary flow following treatment with the extract, as compared with placebo (*22–26*, *28*, *31*). However, in one study with only a small number of patients, no beneficial urodynamic effects were seen (*27*). Ten of these trials also demonstrated significant improvements in the symptoms of nocturia, daytime polyuria, dysuria, and the hesitancy and urgency of micturition, as compared with placebo (*22–26*, *28*, *30*, *31*, *33*, *34*).

A histological study of prostate tissue biopsies from patients with BPH before and after treatment (75 mg extract daily for 1–3 months) showed that a lipophilic extract of the trunk bark enhanced prostate secretion, but did not reduce the size of the prostate (*50*). A lipophilic extract of the trunk bark also restored the activity of prostate acid phosphatase and the normal levels of total protein secretion from the prostate in patients with abnormally low levels of secretion (*51*).

Comparative studies

Four double-blind studies compared oral administration of a lipophilic extract of the crude drug and docosanol (one of the active constituents of the extract) with an extract of Radix Urticae Urtae, sitosterin, non-steroidal anti-inflammatory drugs and antibiotics (*22*, *52*, *53*). The total number of patients was 183, with a range of 39–53 patients per study. Patients were treated with either 100 mg docosanol, 100 mg trunk bark extract or varying doses of the compara-

tive drugs. Improvements in postvoid residual volume, nocturia, daytime polyuria and the urgency of micturition were seen in all treatment groups in three studies, with the trunk bark extract appearing to be the most effective (*22*, *52*, *53*). However, no controlled studies have yet been performed to compare the effects of trunk bark extracts with newer agents (e.g. finasteride or α_1-receptor antagonists, such as alfuzosin) for the treatment of BPH symptoms.

Clinical trials without controls

Fourteen clinical trials without controls demonstrated an improvement of global outcome assessments after oral treatment with a chloroform extract of the trunk bark in 461 men with stage I or II BPH (*54–67*). In four of these studies, a total of 180 patients received 75 mg extract daily for 21 days to 3 months (*54*, *56*, *64*, *66*); in the other 10 studies, a total of 281 patients were treated with 100 mg extract daily for 21 days to 3 months (*55*, *57–63*, *65*, *67*). In all but three studies (*59*, *63*, *67*), the global outcome was assessed as either improved, good, very good or excellent in over 50% of the patients.

The results of 19 clinical trials without controls involving 849 men with BPH (18–59 patients per study) demonstrated an objective improvement in their symptoms following treatment with a lipophilic extract of the trunk bark (*53*, *68–85*). Patients were treated daily with either 75 mg (116 patients), 75–100 mg (20 patients), 100 mg (523 patients), 150 mg (42 patients) or 200 mg extract (148 patients) for 20–160 days. Improvements in nocturia, daytime polyuria, postvoid residual volume and mean maximum urinary flow rate were observed in over 50% of patients in 14, eight, seven and four studies, respectively. Other symptoms such as dysuria, and hesitancy and urgency of micturition also improved (*44*).

A large open-label study assessed improvements in urodynamic parameters in 500 men with BPH after daily treatment with a lipophilic extract of the bark for over 5 years (doses not specified). Improvements in dysuria, daytime polyuria and nocturia were observed in over 68% of patients, and improvements in urinary flow rate and volume were reported in over 61% (*32*). The greatest improvements were observed in patients with moderate symptoms, who did not have a prominent median lobe of the prostate, and whose baseline postvoid residual volume was less than 100 ml (*32*, *44*). An improvement in prostate secretion was also reported, but only in the absence of prostate infection (*38*).

A multicentre study without controls assessed the efficacy and safety of treatment with a trunk bark extract (50 mg) twice daily for 2 months in 85 men with symptoms of BPH (neither the extract nor the stage of BPH was described). Subjective assessment of the outcomes was made using the International Prostate Symptom Score (IPSS) and the Quality of Life score (QL), and urine flowmetry was used for objective evaluation. After treatment, the IPSS and QL improved significantly ($P < 0.001$) by 40% and 31%, respectively. Nocturnal frequency was also significantly reduced by 32% ($P < 0.001$) (*55*).

Contraindications

Cortex Pruni Africanae is contraindicated in cases of known allergy to plants of the Rosaceae family. It is also contraindicated during pregnancy and lactation and in children under the age of 12 years because of its effects on androgen and estrogen metabolism (*39*, *86*).

Warnings

Cortex Pruni Africanae relieves the symptoms associated with BPH, but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or if blood appears in the urine or acute urinary retention occurs, contact a physician.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A lipophilic extract of Cortex Pruni Africanae had no effect on fertility in male rats and rabbits at doses up to 80 mg/kg body weight daily (*44*). No mutagenic or clastogenic activity has been observed in vitro or in vivo (*44*).

Pregnancy: teratogenic effects

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during pregnancy.

Pregnancy: non-teratogenic effects

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during pregnancy.

Nursing mothers

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during lactation.

Paediatric use

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae in children.

Other precautions

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions.

Adverse reactions

Data from clinical studies show that a lipophilic extract of Cortex Pruni Africanae is well tolerated in humans. A few cases of minor transient gastro-

intestinal side-effects, such as diarrhoea, gastric pain and nausea, were reported in two clinical trials (*22*, *23*), and single cases of constipation, dizziness and visual disturbance were also reported (*23*).

Dosage forms

Lipophilic extract of the crude drug (*1*, *2*). Store in a cool, dry place.

Posology

(Unless otherwise indicated)
Daily dosage: 75–200 mg lipidosterolic extract of the crude drug, in divided doses. To minimize gastrointestinal disturbances, take with food or milk.

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Cortex Rhamni Purshianae

Definition

Cortex Rhamni Purshianae consists of the dried bark of *Rhamnus purshiana* D.C. (Rhamnaceae) (*1–5*). Cascara (*2*) and Cascara Sagrada (*5*) are also official names of the drug.

Synonyms

Frangula purshiana (D.C.) A. Gray ex J.C. Cooper (*3*, *5*), *Rhamnus purshianus* D.C. (*4*). Although the species name in the British, French, German and European pharmacopoeias is given as *purshianus*, the correct species name is *purshiana* according to the *International code of botanical nomenclature* (Tokyo code) (*4*; J. Morley, personal communication, 1998).

Selected vernacular names

Amerikanischen Faulbaum, bear wood, bitter bark, cascara bark, cascararinde, chittem bark, cortex cascara sagradae, écorce de cascara, purshiana bark, quishron moquaddas, Rhamnus, sacred bark (*1*, *6–8*).

Geographical distribution

Indigenous to south-western Canada and the Pacific north-west of the United States of America (*8–10*).

Description

A tree, 4–10 m high, with reddish-brown bark and hairy twigs. Leaves petiolate, elliptical, acuminate, serrulate, or sometimes entire, with 10–15 pairs of veins, dull green upper surface and pubescent underside. Inflorescence an axillary umbellate cyme of small greenish flowers. Fruit a turbinate, purplish-black drupe, about 8 mm long, composed of 3 indehiscent cocci (*8*).

Plant material of interest: dried bark

The fresh bark contains free anthrones and must be dried for at least 1 year or artificially aged by heat or aeration before therapeutic use (*1*, *5*, *8*).

General appearance

Occurs in quills, slightly channelled or nearly flat pieces; usually 1–5 mm thick, usually varying greatly in length (up to 20 cm) and width (up to 2 cm). Outer surface brown, purplish-brown or brownish-red, usually more or less completely covered by a whitish coat of lichens, epiphytic moss and foliaceous liverwort; shows occasional lenticels that are orientated transversally. Inner surface light yellow to reddish-brown or almost black, with fine longitudinal striations; turns red when treated with dilute alkali (Bornträger's test). Fracture short and granular in outer part and somewhat fibrous in the inner part (*1*, *3*, *5*).

Organoleptic properties

Odour: faint, but characteristic; taste: bitter, nauseous and persistent (*1*, *11*).

Microscopic characteristics

Cork frequently bearing dense masses of lichen tissues, and formed of 10 or more rows of small, flattened, thin-walled cells with yellowish-brown contents. Cortex narrow, yellowish-grey, consisting of a few layers of collenchyma and several layers of parenchyma, containing starch granules and scattered cluster crystals of calcium oxalate; showing numerous scattered, bright, ovoid groups of sclereids, usually encircled by cells containing prismatic crystals of calcium oxalate. Phloem brownish-yellow, traversed by numerous wavy medullary rays (1–5 cells wide and 15–25 cells deep); consists of alternating bands of lignified fibres, surrounded by crystal sheath containing prismatic crystals of calcium oxalate, and of soft sieve tissue and parenchyma with brown walls; contains scattered cluster crystals of calcium oxalate and starch grains; each fibre 8–15 µm in diameter. Groups of sclereids also found in outer part of phloem; sclereids possess thick, stratified, pitted walls. Parenchyma may contain yellow substance which turns crimson with dilute alkali (Bornträger's test) (*1*, *5*).

Powdered plant material

Yellowish-brown to dusky yellowish-orange. Bundles of partly lignified phloem fibres accompanied by crystal sheaths containing prismatic crystals of calcium oxalate; groups of sclereids accompanied by crystal sheaths; cluster crystals of calcium oxalate, 5–20 µm, occasionally up to 45 µm, in diameter; some parenchymatous cells contain yellow substance which turns crimson when treated with dilute alkali (Bornträger's test); cork cells and frequently epiphytes—latter may be liverworts (entire or in fragments, having a lamina one cell thick without a midrib and composed of isodiametric cells) or mosses (having a lamina 1 cell thick composed of elongated cells and possessing a midrib several cells thick); starch grains spheroid, up to 8 µm in diameter (*1*, *3*, *5*).

General identity tests

Macroscopic, microscopic and microchemical (Bornträger's test) examinations (*1*, *3*, *5*) and thin-layer chromatography for characteristic hydroxyanthracene glycosides (*3*, *12*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign matter

Not more than 1% (*3*).

Total ash

Not more than 7% (*1*, *3*).

Water-soluble extractive

Not less than 23% (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

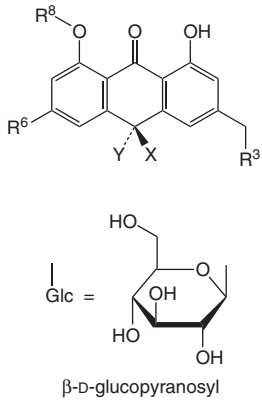
Chemical assays

Contains not less than 8.0% hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both calculated as cascaroside A. Quantitative analysis is performed by spectrophotometry at 515 nm (*3*, *5*). A high-performance liquid chromatography method for the quantitative analysis of cascarosides has been reported (*16*).

Major chemical constituents

The active constituents are hydroxyanthracene glycosides (6–9%). Of these, 70–90% are C-10 glycosides, with the 8-*O*-glycosides, aloins A and B, and 11-desoxyaloins A and B (chrysaloins A and B) accounting for 10–30%. The diastereoisomeric pairs, cascarosides A and B and cascarosides C and D and cascarosides E and F constitute 60–70% of the total *O*-glycosides. Other major hydroxyanthracene glycosides (10–20%) include the hydroxyanthraquinones, chrysophanol-8-*O*-glucoside and aloe-emodin-8-*O*-glucoside (*7*, *17–19*).

In the fresh bark, anthraquinones are present in the reduced form, and are converted by oxidation from their corresponding parent anthraquinone glycosides during drying and storage (*10*). The structures of the major anthracene glycosides are presented below.



	X	Y	R^3	R^6	R^8
aloin A	Glc	H	OH	H	H
aloin B	H	Glc	OH	H	H
cascaroside A	Glc	H	OH	H	Glc
cascaroside B	H	Glc	OH	H	Glc
cascaroside C	Glc	H	H	H	Glc
cascaroside D	H	Glc	H	H	Glc
cascaroside E	Glc	H	H	OH	Glc
cascaroside F	H	Glc	H	OH	Glc
chrysaloin A	Glc	H	H	H	H
chrysaloin B	H	Glc	H	H	H

Medicinal uses

Uses supported by clinical data

Short-term treatment of occasional constipation (*8*, *17*, *20*, *21*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a cathartic (*1*).

Uses described in folk medicine, not supported by experimental or clinical data

Internally for treatment of diabetes and externally for skin irritations (*6*).

Pharmacology

Experimental pharmacology

Laxative effects

The laxative effects of Cortex Rhamni Purshianae are due primarily to the anthraquinone glycosides and cascarosides A–D (*7*, *22*). After oral administration of Cortex Rhamni Purshianae, the hydroxyanthracene glycosides are not absorbed in the upper intestine, but are hydrolysed in the colon by intestinal bacteria to form the pharmacologically active metabolites. These metabolites are partially absorbed in the colon and act as a stimulant and irritant to the gastrointestinal tract, as does senna (*21*, *23–25*). The mechanism of action, similar to that of senna, is twofold. Firstly, there is stimulation of colonic motility, resulting in increased propulsion and accelerated transit of faeces through the colon (which reduces fluid absorption from the faecal mass). Secondly, there is an increase in paracellular permeability across the colonic mucosa, probably due to inhibition of sodium/potassium-transporting adenosine triphosphatase or inhibition of chloride channels (*23*, *26*). The increased permeability results in increased water content in the colon (*21*, *26*).

The laxative effect of Cortex Rhamni Purshianae is not generally observed until 6–8 hours after oral administration. Hydroxyanthracene glycosides are excreted predominantly in the faeces but are also excreted to some extent in urine, producing an orange colour; anthrones and anthranols will also pass into breast milk (*23*).

Toxicity and overdose

As with other anthraquinone laxatives, the major symptoms of overdose are intestinal pain and severe diarrhoea with consequent loss of fluid and electrolytes (*27*). Treatment of overdoses should be supportive with generous amounts of fluid. Electrolyte levels should be monitored, particularly those of potassium. This is especially important in children and the elderly (*27*).

Clinical pharmacology

None.

Contraindications

Cortex Rhamni Purshianae should not be administered to patients with intestinal obstruction and stenosis, atony, inflammatory diseases of the colon (such as ulcerative colitis, irritable bowel syndrome, Crohn disease), appendicitis,

severe dehydration with water and electrolyte depletion, or chronic constipation (*20*, *24*, *27*). As with other stimulant laxatives, Cortex Rhamni Purshianae is contraindicated in patients with cramps, colic, haemorrhoids, nephritis or any symptoms of undiagnosed abdominal disorders such as pain, nausea or vomiting (*27*). Owing to the pronounced action on the large intestine and insufficient toxicological investigations, Cortex Rhamni Purshianae and other anthranoid laxatives should not be administered to pregnant women (*28*, *29*). As anthranoid metabolites may appear in breast milk, Cortex Rhamni Purshianae should not be used during lactation, since there are insufficient data to assess potential pharmacological effects in the breastfed infant (*29*). Use of Cortex Rhamni Purshianae in children under 10 years is contraindicated (*20*).

Warnings

Products containing Cortex Rhamni Purshianae should only be used if no effect can be obtained through a change of diet or by the use of bulk-forming laxatives. Patients should also be warned that certain constituents of the bark are excreted by the kidney and may colour the urine orange, which is harmless. Cortex Rhamni Purshianae and other stimulant laxatives should not be used in patients with abdominal pain, nausea or vomiting. The use of stimulant laxatives for longer than 2 weeks requires medical supervision. Rectal bleeding or failure to have a bowel movement after taking a laxative may indicate a serious condition. Chronic use may result in aggravation of constipation with laxative dependence, a need for increased dosages and disturbances of water and electrolyte balance (e.g. hypokalaemia). Chronic use may also lead to colonic dysfunction (atonicity) and melanotic pigmentation of the colonic mucosa (pseudomelanosis coli), which is harmless. Laxative abuse resulting in diarrhoea and consequent fluid and electrolyte losses (mainly of potassium) may cause albuminuria, haematuria, and cardiac and neuromuscular dysfunction. Neuromuscular dysfunction may arise particularly in the case of concomitant use of cardiotonic glycosides (e.g. digoxin, digitalis or strophanthin), diuretics, corticosteroids or liquorice root (*27*).

Precautions

General

Cortex Rhamni Purshianae and other laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, because of the risk of electrolyte imbalance (*27*).

Drug interactions

Increased intestinal transit time may result in reduced absorption of orally administered drugs (*30*). Electrolyte imbalances, such as hypokalaemia, may potentiate the effects of cardiotonic glycosides (e.g. digoxin, digitalis or

strophanthin). Hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs (e.g. quinidine) that change sinus rhythm by affecting potassium channels. Hypokalaemia caused by drugs such as thiazide diuretics, adrenocorticosteroids or liquorice root may be enhanced, and electrolyte imbalance may be aggravated (*21*).

Drug and laboratory test interactions

Anthranoid metabolites may not be detectable in faeces or urine by standard methods. Thus faecal excretion measurements may not be reliable (*30*). Urinary excretion of certain anthranoid metabolites may cause discoloration of the urine which is not clinically relevant, but may cause false-positives in urinary urobilinogen tests and in estrogen measurements using the Kober procedure (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Although chronic use of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer, no causal relationship has been demonstrated (*32–35*).

No specific data on carcinogenicity or mutagenicity are available for Cortex Rhamni Purshianae or the cascarosides. Data for aloin derived from aloe indicate no genotoxic risk. Emodin derived from aloe showed both positive and negative results in vitro, but was negative in vivo. Emodin was mutagenic in the *Salmonella*/microsome assay, but gave inconsistent results in gene mutation assays (V 79). It showed positive results in the test for unscheduled DNA synthesis with primary rat hepatocytes, but negative results in the sister chromatid exchange assay (*20*).

Pregnancy: teratogenic effects

See Contraindications. Administration of aloin A to rats at doses up to 200 mg/kg body weight had no embryotoxic, teratogenic or fetotoxic effects (*36*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Adverse reactions

Single doses of Cortex Rhamni Purshianae may result in cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage (*21*).

Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools.

Long-term laxative abuse may lead to electrolyte imbalance (hypokalaemia and hypocalcaemia), metabolic acidosis, malabsorption of nutrients, weight loss, albuminuria and haematuria (*37*, *38*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Secondary aldosteronism may occur after prolonged use due to renal tubular damage. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported after long-term laxative abuse (*39*). Pseudomelanosis coli has been observed in individuals taking anthraquinone laxatives for extended time periods (*27*, *38*). The pigmentation is harmless and usually reversible within 4–12 months after the drug is discontinued (*38*). Conflicting data exist on other toxic effects after long-term use such as intestinal-neuronal damage (*38*, *40*). In incontinent patients using anthranoid laxatives, prolonged exposure of the skin to faeces may cause skin damage (*41*).

Use of the fresh bark of *Rhamnus purshiana* may cause severe vomiting, with possible abdominal spasms (*23*). One case of occupational asthma and rhinitis has been reported (*42*).

Dosage forms

Finely cut crude drug, powder, dried extracts, extract (*5*), fluidextract (*5*), other liquid and solid preparations (*5*, *7*). Store in a tightly sealed, light-resistant container (*1*, *3*).

Posology

The correct dosage for the treatment of occasional constipation is the smallest dosage necessary to maintain a soft stool. Daily dosage: 0.3–1.0 g crude drug in a single dose (*20*); all preparations standardized to contain 20–30 mg of hydroxyanthracene derivatives calculated as cascaroside A; taken at bedtime, or in two divided doses, one in the morning and one at bedtime (*20*, *21*).

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Flos Sambuci

Definition

Flos Sambuci consists of the dried flowers of *Sambucus nigra* L. (Caprifoliaceae) (*1–3*).

Synonyms

Sambucus arborescens Gilib., *S. medullina* Gilib., *S. vulgaris* Lam. (*4*).

Selected vernacular names

Aalhornblüten, aghti, agti, American elder bailasan, black elder, bodzavirág, bombardie, boumbardelia, boumbardier, bourtree flower, couloubrignier, elderberry, elder flowers, European elder, fiore di sambuco, fleurs de sureau, Fliederblüten, flor de sabugeiro, flores de sauco, flores sambuci, flos sambuci nigra, Holderblüten, Hollerblüten, Holunderblüten, Hüschenblumen, kabiu sabugah, Kalikenblumen, Khaman kabiv sabubah, okkez sidi musa, patlanguc, petadou, sabugeiro, sahuquier, sahus sambequie, sambuc, sambuco, sammuch, sammuco, sauci, saucio, sauco, sauguer, seic, seiyouniwatoko, sultanotu, sureau, sureau noir, sweet elder (*4–8*).

Geographical distribution

Indigenous to North Africa, North America, western and central Asia and Europe (*6*, *7*).

Description

A shrub growing in moist soil with stems up to 4 m high; contains abundant white pith. Leaves imparipinnate with 5–11 oblong, glabrous leaflets, the lower leaves often 3-lobed. Inflorescence a flat compound cyme. Flowers small, urn-shaped, white, each with 5 minute calyx lobes; corolla 5-cleft gamopetalous, 5 stamens and a tricarpellate pistil with 3 stigmas. Fruits black-purple, edible, berry-like drupes (*6*).

Plant material of interest: dried flowers

General appearance

Inflorescence a flat compound cyme. Flowers white, up to 5 mm in diameter, has 3 small bracts (visible with a hand lens) and may have a peduncle. Calyx

minute, 5-lobed; corolla light yellow, with 5 broadly oval petals fused at their bases into a tube, 5 yellow stamens with short filaments and lemon-yellow anthers, and a trilocular inferior ovary; ovary bears a short style with 3 obtuse stigmata; filaments of the 5 stamens alternate with the petals. Corolla often isolated or fused to base of the stamens (*1*, *2*).

Organoleptic properties

Odour: strong, characteristic, aromatic; taste: mucilaginous, sweet but slightly bitter (*1*, *9*).

Microscopic characteristics

Cells of upper epidermis of sepals polygonal with faintly striated cuticle; cells of lower epidermis sinuous-walled with strongly striated cuticle and scattered, rounded, anomocytic stomata; unicellular marginal teeth rounded at the apex occur in the basal region of sepal. Cells of upper epidermis of petals polygonal with slightly thickened, beaded walls and striated cuticle; cells of lower epidermis distinctly sinuous with large, rounded, anomocytic stomata. Numerous small globules of essential oil in the epidermis of sepals and petals. Mesophyll of sepals and petals contains idioblasts of numerous small, sandy crystals of calcium oxalate. Fibrous layer of anthers with characteristic thickening and beading on walls; pollen grains subspherical, 17–24 µm in diameter, with smooth exine, 3 distinct pores and 3 furrows (*1*).

Powdered plant material

Greenish-yellow. Numerous spherical, sometimes ellipsoidal, pollen grains up to 30 µm in diameter, with 3 germinal pores and very finely pitted exine; calyx epidermal cells with a striated cuticle and occasional unicellular marginal teeth from basal region; corolla fragments with numerous small globules of essential oil; cells of corolla upper epidermis with slightly thickened, beaded walls and striated cuticle; mesophyll cells of sepals and petals with idioblasts containing numerous sandy crystals of calcium oxalate (*2*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for constituent phenolic acids and flavonoids (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 8% fragments of coarse pedicels and other foreign matter; not more than 15% discoloured, brown flowers (*2*).

Total ash

Not more than 10% (*1*, *2*).

Acid-insoluble ash

Not more than 2% (*1*).

Water-soluble extractive

Not less than 25% (*1*).

Loss on drying

Not more than 10% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

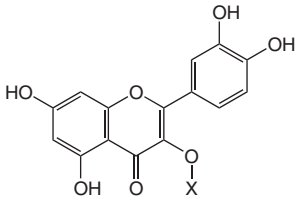
Chemical assays

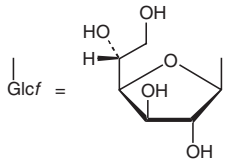
Contains not less than 0.80% flavonoids, calculated as isoquercitrin, as determined by spectrophotometry at 425 nm (*2*).

Major chemical constituents

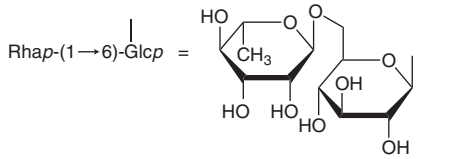
The major characteristic constituents (up to 3.0%) are the flavonoids (kaempferol, astragalin, quercetin, rutin, isoquercitrin, hyperoside). Other

major secondary metabolites include about 1% triterpenes (α- and β-amyrin, ursolic acid, oleanolic acid), about 1% sterols (β-sitosterol, campesterol, stigmasterol), about 3% phenolic acids and their corresponding glycosides (chlorogenic, ferulic, caffeic and *p*-coumaric acids), and up to 0.15% essential oil (*4*, *5*, *7*, *13*). The structures of the representative major constituents are presented below.

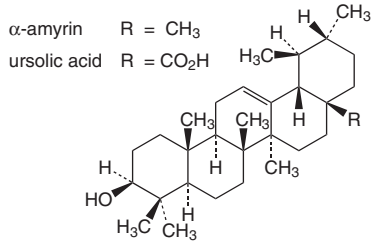


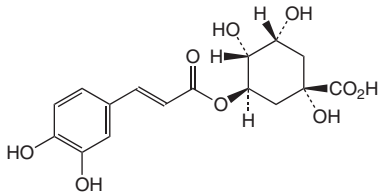


β-D-glucofuranosyl



O-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl





chlorogenic acid

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As a diaphoretic for treatment of fever and chills, and as an expectorant for treatment of mild inflammation of the upper respiratory tract. Also for symptomatic treatment of the common cold (*1*, *7*, *14*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of conjunctivitis, constipation, diabetes, diarrhoea, dry skin, headaches and rheumatism (*5*, *13*, *15*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

An 80% ethanol extract of Flos Sambuci had moderate anti-inflammatory activity in rats: it inhibited carrageenan-induced footpad oedema by 27%. The extract was administered intragastrically (100 mg/kg body weight) 1 hour prior to administration of carrageenan. The control drug, indometacin (5 mg/kg body weight) inhibited carrageenan-induced footpad oedema by 45% (*16*). Intraperitoneal administration of an unsaponifiable fraction of the flowers to mice moderately enhanced phagocytosis at a dose of 0.5 ml/animal (*17*). A 100% methanol extract of the flowers inhibited the biosynthesis of the inflammatory cytokines interleukin-1α, interleukin-1β and tumour necrosis factor-α at a concentration of 30 µg/ml in human peripheral mononuclear cells in vitro (*18*).

Diuretic activity

Intragastric administration of an infusion of the flowers (20 ml/kg body weight) or of a potassium- and flavonoid-rich extract of the flowers had a diuretic effect in rats which was greater than that observed with theophylline (5 mg/kg body weight) (*19*).

Clinical pharmacology

Diaphoretic activity

Flos Sambuci is reported to increase the response of the sweat glands to heat stimuli (*7*, *20*, *21*), and increase diaphoresis in healthy subjects (*7*, *21*).

Contraindications

No information available.

Warnings

No information available.

Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Sambuci should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

No information available.

Dosage forms

Crude drug for decoctions and infusions (crude drug also available in tea bags); as a component of multi-ingredient products (*7*). Store in a well-closed container, protected from light (*2*).

Posology

(Unless otherwise indicated)
Daily dosage: crude drug 3–5 g as an infusion (preferably taken hot) three times daily; 25% ethanol extract 3–5 ml; tincture (1 : 5 in 25% ethanol) 10–25 ml (*22*).

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Radix Senegae

Definition

Radix Senegae consists of the dried roots and root crowns of *Polygala senega* L., *Polygala senega* L. var. *latifolia* Torrey et Gray, or other closely related *Polygala* species (Polygalaceae) (*1–3*).

Synonyms

Polygala senegum L. (*1*), *P. rosea* Steud., *Senega officinalis* Spach (*4*).

Selected vernacular names

Bambara, bulughâ lon, gizr uththuban, Klapperschlangenwurzel, mountain flax, peuhl, polygala de virginie, racine de polygala, racine de senega, Radix polygalae, Radix polygalae senegae, rattlesnake root, seneca snakeroot, Senegakreuzblume, senega root, senega snakeroot, Senegawurzel, snake root, szenega gyökér, tsuknida, vahulill, virginische Schlangenwurzel, yoruba (*1–3*, *5–7*).

Geographical distribution

Indigenous to eastern Canada and north-eastern United States of America (*6–8*).

Description

A perennial herbaceous plant with numerous stems sprouting from a single thick gnarled crown arising from a conical, twisted, branched yellow root. Aerial portion consists of several erect or ascending, smooth stems up to 15–40 cm high, bearing alternate, lanceolate or oblong-lanceolate leaves with serrulate margins. Inflorescence a spike of small, white flowers, which are almost sessile with rounded-obovate wings, concave with a short crested carina (*1*, *7*).

Plant material of interest: dried roots and root crowns

General appearance

Root crown greyish-brown, wider than the root; diameter of the root crown up to 3 cm, gradually tapering to the tip; surface transversely and longitudinally striated, often shows a more or less distinct decurrent, elongated spiral keel. Forms an irregular head consisting of numerous remains of stems and tightly

packed purplish-brown to red buds. Taproot, 0.5–1.5 cm in diameter and 3–20 cm in length, brown to yellow, occasionally branched, sometimes flexuous, usually without secondary roots, except in the Japanese varieties and species, which contain numerous fibrous branched rootlets. Fracture short and shows a yellowish cortex of varying thickness surrounding a pale central woody area somewhat circular or irregular in shape, depending on the species (*1–3*).

Organoleptic properties

Odour: characteristic, faint, sweet, slightly rancid or reminiscent of methyl salicylate, sternutatory when in powder form; taste: sweet, subsequently acrid and irritating to the throat (*1–3*).

Microscopic characteristics

Cork layer consisting of several rows of light-brown cork cells; secondary cortex composed of parenchyma cells and sieve tubes, traversed by medullary rays, 1–3 cells wide. Phelloderm of slightly collenchymatous cells containing droplets of oil. Phloem and xylem arrangement usually normal, especially near the crown, but where a keel is present, it is formed by increased development of phloem; other anomalous secondary development sometimes occurs, resulting in formation of 1 or 2 large wedge-shaped rays in phloem and xylem, the parenchymatous cells of which contain droplets of oil. Xylem usually central, consists of vessels up to 60 µm in diameter associated with numerous thin-walled tracheids and a few small lignified parenchymatous cells. Starch grains and calcium oxalate crystals absent (*1–3*).

Powdered plant material

Light brown. Longitudinal fragments of lignified tissue made up of pitted tracheids and somewhat larger vessels with numerous bordered pits or with reticulate thickening; yellowish parenchyma and collenchymatous cells containing droplets of oil; occasional fragments of cork and epidermal tissue with stomata and unicellular trichomes from bud scales. Calcium oxalate crystals and stone cells are absent (*1–3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), chemical tests and froth formation (*1*, *2*), and thin-layer chromatography for the presence of saponins (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

Foreign organic matter

Not more than 2% stems and not more than 1% other foreign matter (*2*).

Total ash

Not more than 6% (*3*).

Acid-insoluble ash

Not more than 2% (*1*, *2*).

Alcohol-soluble extractive

Not less than 30% in 20% alcohol (*2*).

Loss on drying

Not more than 13% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*) and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*10*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash and water-soluble extractive tests to be established in accordance with national requirements.

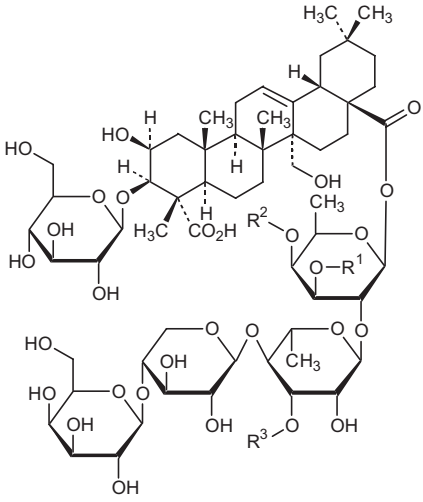
Chemical assays

Quantitative analysis of triterpene saponins by high-performance liquid chromatography (*11*).

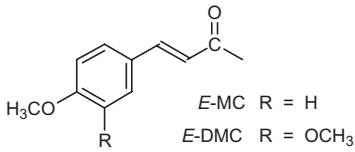
Major chemical constituents

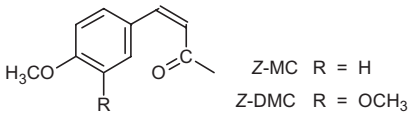
Methyl salicylate (0.1–0.3%), the compound responsible for the characteristic odour of the drug (*12*). The major reported biologically active constituents are triterpene saponins (6–16%) (*6*, *8*, *13*). The saponins are 3-glucosides of

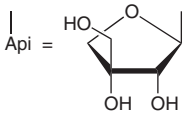
presenegenin, which also contain at C-28 an oligosaccharide chain that has a fucose moiety esterified with 3,4-dimethoxycinnamic or 4-methoxycinnamic acid (*14–16*). The structures of the representative saponins are presented below.



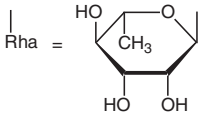
	R^1	R^2	R^3
(*E*)-senegasaponin A	H	*E*-MC	Api
(*Z*)-senegasaponin A	H	*Z*-MC	Api
desacylsenegasaponin A	H	H	Api
(*E*)-senegasaponin B	H	*E*-MC	H
(*Z*)-senegasaponin B	H	*Z*-MC	H
senegin II	H	*E*-DMC	H
(*Z*)-senegin II	H	*Z*-DMC	H
desacylsenegin II	H	H	H
(*E*)-senegin III	Rha	*E*-MC	H
(*Z*)-senegin III	Rha	*Z*-MC	H
desacylsenegin III	Rha	H	H







D-*apio*-β-D-furanosyl



6-deoxy-α-L-mannopyranosyl

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As an expectorant for symptomatic treatment of coughs due to bronchitis, emphysema and catarrh of the upper respiratory tract (*1*, *6*, *14*, *17–19*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, asthma, constipation, rheumatism and snake bites (*5*).

Pharmacology

Experimental pharmacology

Expectorant activity

Intragastric administration of a fluidextract of Radix Senegae (0.1–10 ml/kg body weight) enhanced the production of respiratory tract fluid in decerebrate or anaesthetized animals. Three to four hours after administration, the output of respiratory tract fluid increased by up to 173% in cats and 186% in guinea-pigs, but no effect was observed in rabbits (*20*). In another study, administration of a syrup of the root to anaesthetized dogs significantly increased the volume of respiratory tract fluid within 5–30 minutes ($P < 0.001$); after 2 hours, the fluid volume in the treatment group was 0.114 ml as compared with 0.01 ml in control animals treated with saline (*21*). Intragastric administration of a 50% methanol extract of the root (2 g/kg body weight) inhibited stress-induced gastric ulcers in rats by 98.5% (*22*). Intragastric administration of an aqueous suspension of a 50% methanol extract of the root (2 g/kg body weight) to rats reduced congestive oedema by 62% and significantly increased the 24-hour urine volume as compared with control animals ($P < 0.01$) (*23*).

Effect on blood cholesterol and triglyceride levels

Intraperitoneal administration of an *n*-butanol extract of the root (5 mg/kg body weight) reduced blood triglyceride levels in mice fed a normal diet, and reduced blood cholesterol and triglyceride levels in mice fed a high cholesterol diet (*24*).

Antihyperglycaemic activity

Intraperitoneal administration of an *n*-butanol extract of the roots (10 mg/kg body weight) reduced blood glucose levels in healthy mice and in mice with streptozocin-induced hyperglycaemia (*25*). Intragastric administration of a saponin fraction of a root extract reduced glucose-induced hyperglycaemia in rats at a dose of 200 mg/kg body weight (*16*). Intraperitoneal administration of a saponin fraction of a root extract (25 mg/kg body weight) significantly increased the plasma levels of adrenocorticotropic hormone, cortisone and glucose in rats ($P < 0.01$) (*26*). Intragastric administration of a 100% methanol extract of the root decreased the absorption of ethanol in rats (500 mg/kg body weight) (*15*).

Toxicity

The LD_{50} of the root was 17 g/kg body weight after intragastric administration to mice. The LD_{50} of the root bark was 10 g/kg body weight and that of the root core (which had the lowest saponin concentration of the three root samples) was 75 g/kg body weight (*13*).

Clinical pharmacology

Expectorant activity

The expectorant activity of the crude drug is due to the constituent saponins which produce local irritation of the mucous membranes of the throat and respiratory tract. This irritation stimulates an increase in bronchial secretions, thereby diluting the mucus, reducing its viscosity and facilitating expectoration (*19–21*, *27*, *28*). Saponins may also reduce the surface tension of mucus, thus reducing its viscosity (*29*). Oral administration of a fluidextract of the root was shown to reduce the viscosity of mucus in patients with bronchiectasis (*17*).

Contraindications

Pregnancy (See Precautions).

Warnings

If coughing persists for more than 7 days, seek medical advice. Radix Senegae may exacerbate existing gastrointestinal inflammations such as gastritis or gastric ulcers, and excessive doses may cause vomiting (*30*).

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No mutagenic effects of an aqueous or 50% methanol extract of the root were observed in the *Bacillus subtilis* recombination assay or in the microsome reversion assay in *Salmonella typhimurium* strains TA98 and TA100 (*31*).

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

Traditional uses for Radix Senegae include its use as an emmenagogue (*5*). As extracts of the root have been shown to stimulate uterine contractions in animal models (*32*), Radix Senegae should not be taken during pregnancy.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; nursing mothers; or

paediatric use. Therefore, Radix Senegae should not be administered during lactation or to children without medical supervision.

Adverse reactions

Overdose with Radix Senegae preparations may cause nausea, diarrhoea and vomiting due to gastrointestinal upset (*13*). In sensitive individuals, gastrointestinal upset may occur even at the therapeutic dosage (*33, 34*).

Dosage forms

Chopped crude drug for decoctions and extracts (*6, 18*). Store in a tightly closed container, protected from light and humidity (*3*).

Posology

(Unless otherwise indicated)
Daily dosage: 1.5–3.0 g crude drug as an infusion or decoction in divided doses (*18, 35*). A 60% ethanol extract (made slightly alkaline with dilute ammonia): 0.9–3 ml; tincture: 2.5–7.5 g. Equivalent preparations (*18*).

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Fructus Serenoae Repentis

Definition

Fructus Serenoae Repentis consists of the dried ripe fruits of *Serenoa repens* (Bartr.) Small. (Arecaceae) (*1–3*).

Synonyms

Brahea serrulata (Michx.) H. Wendl., *Chamaerops serrulata* Michx., *Corypha repens* Bartr., *Sabal serrulata* (Michx.) Nichols, *Sabal serrulata* (Michx.) Nuttall. ex Schult., *Serenoa serrulata* Hook., *Serenoa serrulata* Roem. et Schult., *Serenoa serrulatum* (Michx.) Benth et Hook, *Serenoa serrulatum* Schult. (*1, 3–5*).

Selected vernacular names

American dwarf palm tree, dwarf palm tree, dwarf palmetto, fan palm, sabal, sabal fructus, Sägepalmenfrüchte, saw palmetto, saw palmetto berries, serenoa (*1, 2, 5, 6*).

Geographical distribution

Indigenous to the south-east of the United States of America, from South Carolina to Florida (*2, 6*).

Description

Low scrubby palm growing in sandy soil, with characteristic creeping rhizome, one end of which rises a short distance above ground, surrounded by a dense crown of leaves with saw-like margins. Petioles slender and spinose on edges; blade fan-shaped, with palmate divisions that are slightly cleft at the summit. Inflorescence densely tomentose and shorter than the leaves. Fruit a 1-seeded drupe (*6*).

Plant material of interest: dried ripe fruits

General appearance

Drupe superior, ellipsoidal, ovoid or somewhat globular, 1.5–3.0 cm long, 1.0–1.5 cm in diameter; dark brown to black with a smooth, dull surface, somewhat oily, with a few large, angular depressions and ridges due to contraction of the

inner layer on drying; summit marked by remains of style; base marked by stem-scars or has remains of stem. Epicarp and sarcocarp together form a thin coriaceous shell enclosing a hard but thin endocarp; endocarp externally reddish-brown and somewhat fibrous, as is inner layer of the sarcocarp; inner layer of endocarp smooth, enclosing an ellipsoidal or ovoid, hard somewhat flattened, anatropous, reddish-brown seed marked on the raphe side by an arillus-like appendage and marked on the opposite side near the end by the micropyle, which forms a slight projection; has a large endosperm of thick-walled parenchyma and a very small embryo at the micropyle (*2*, *3*, *6*).

Organoleptic properties

Odour: pronounced, aromatic, fruity; taste: sweetish, aromatic, slightly acrid (*6*).

Microscopic characteristics

Sarcocarp covered by a small-celled, thin-walled epidermis. Outermost layers of pulp wall contain yellowish-brown or brownish-red substances; inner layers have scattered single cells containing brown substances; occasional large, thick-walled, punctate stone cells with wide lumens. Innermost layer of sarcocarp wall consists almost completely of thick-walled, punctate, irregularly shaped stone cells. Outer layer of the seed coat consists of thick-walled large cells; cells in middle layer smaller and thin-walled; cells of innermost layer small and flattened; contents of all seed-coat cells non-punctate brown. Outer endosperm cells radially elongated, coarse-walled and inner cells larger, thick-walled and coarsely punctate. Vascular bundles accompanied by fibres with stigmata which have siliceous solids attached (*3*, *6*).

Powdered plant material

Yellowish-brown. Fragments of sarcocarp, the cells of which contain yellowish-brown or brownish-red amorphous substances; whitish fragments of endosperm, the cell walls considerably thickened and with large pores; occasional stone cells, nearly colourless, more or less tabular or irregular in shape, up to 140 µm in length, with walls about 15 µm thick, showing numerous simple or branching pores (*2*, *6*).

General identity tests

Macroscopic and microscopic examinations (*2*, *3*, *6*), and thin-layer chromatography (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*8*).

Foreign organic matter

Not more than 2% (*2*, *3*).

Total ash

Not more than 5% (*3*).

Acid-insoluble ash

Not more than 1% (*2*, *3*).

Water-soluble extractive

Not less than 8% (*2*, *3*).

Loss on drying

Not more than 12% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

Other purity tests

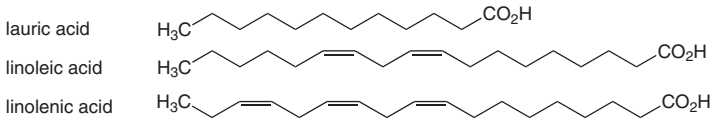
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Quantitation of fatty acids, both free and as their corresponding ethyl esters, by gas chromatography. The total fatty acid content is not less than 9.0%, and the amounts of individual fatty acids are not less than 3.0% oleic, 2.0% lauric, 1.2% myristic, 1.1% palmitic, 0.4% linoleic, 0.2% caphoic, 0.2% caprylic, 0.2% capric, 0.1% palmitoleic, 0.1% stearic and 0.1% linolenic acids (*3*).

Major chemical constituents

The major constituents are free fatty acids and their corresponding ethyl esters; sterols and lipids. The primary fatty acid constituents include oleic, lauric, myristic, palmitic, linoleic, caphoic, caprylic, capric, palmitoleic, stearic and linolenic acids (*5*, *11*, *12*). The major sterols include β-sitosterol, stigmasterol and daucosterol (*13*). The lipids consist of triglycerides of fatty acids. The structures of some of the free fatty acids are presented below.



Medicinal uses

Uses supported by clinical data

Treatment of lower urinary tract symptoms (nocturia, polyuria, urinary retention) secondary to BPH stages I and II, as defined by Alken (*1*, *4*, *14*–*33*), in cases where diagnosis of prostate cancer is negative.

Uses described in pharmacopoeias and in traditional systems of medicine

As a diuretic and to treat an enlarged prostate (*2*).

Uses described in folk medicine, not supported by experimental or clinical data

As an aphrodisiac, a sedative and a nutritional tonic, as well as for the treatment of bronchitis, cystitis, dysmenorrhoea, sore throat and the common cold (*5*).

Pharmacology

Experimental pharmacology

Antispasmodic activity

Both lipid and saponifiable fractions of Fructus Serenoae Repentis reduced norepinephrine-induced contractions in vitro of rat aorta (IC_{50} 0.53 and 0.50 mg/ml, respectively), as well as potassium chloride-induced contractions of rat uterus (EC_{50} 0.35 and 0.43 mg/ml, respectively) (*34*). A 90% ethanol extract of the fruit reduced vanadate-induced contractions of the rat uterus (EC_{50} 11.41 µg/ml). Norepinephrine-induced contractions of rat deferential duct, and potassium chloride-induced contractions of guinea-pig ileum and bladder smooth muscle tissue were reduced by the addition of a 90% ethanol extract of the fruit (0.33 and 0.15 mg/ml, respectively) (*35*).

Anti-inflammatory activity

Intragastric administration of an ethanol extract of the fruit to rats (5.0 g/kg body weight) inhibited carrageenan-induced footpad oedema (*36*). External application of a 90% ethanol extract of the fruit (500 µg) to mice inhibited croton oil-induced ear oedema by 42% (*37*).

Intragastric administration of an *n*-hexane extract of the fruit to rats (10 ml/kg body weight) decreased capillary permeability induced by histamine, compound 48/80 and dextran, and generalized oedema induced by dextran (*38*). A carbon dioxide (supercritical) extract of the fruit inhibited cyclooxygenase and 5-lipoxygenase in vitro (IC_{50} 28.1 and 18.0 µg/ml, respectively) (*39*). A lipidosterolic extract of the fruit inhibited the in vitro production of leukotriene B_4 in human polymorphonuclear neutrophils stimulated with the calcium ionophore A23187 (*40*). An ethanol extract of the fruit also suppressed A23187-stimulated synthesis of leukotriene B_4 (IC_{50} 8.3 µg/ml) and thromboxane B_2 (IC_{50} 15.4 µg/ml) in rat peritoneal leukocytes in vitro (*37*).

Immunostimulatory activity

Intraperitoneal administration of a polysaccharide fraction, isolated from an aqueous extract of the fruit, to mice (10 mg/kg body weight) had immunostimulant activity, as measured by the colloidal carbon clearance test (*41*). An increased rate of phagocytosis by human polymorphonuclear leukocytes was observed in cells treated with a polysaccharide fraction of the extract (10 µg/ml) (*41*).

Anti-gonadotropic effects

n-Hexane extracts of the fruit had anti-androgenic and anti-estrogenic activity in vitro (*42–47*). Dihydrotestosterone and testosterone uptake by cytosolic androgen receptors of human foreskin and other tissues was inhibited by 40.9% and 41.9%, respectively, after treatment of the tissues with the extract (*42*). In another study, the binding of [^{3}H]dihydrotestosterone to both cytosolic and nuclear androgen receptors in cultured human foreskin fibroblasts was inhibited by 90% and 70%, respectively, after treatment of the cells with a sterol fraction of the *n*-hexane extract (IC_{50} 7.1 units/ml) (*43*). An *n*-hexane fruit extract inhibited androgen binding to cytosolic androgen receptors of rat prostatic tissue in a specific and competitive manner (IC_{50} 330.0–367.5 µg/ml) (*44, 45*). However, in contrast to these findings, the same extract did not inhibit the binding of [^{3}H]dihydrotestosterone to androgen receptors in cultured human foreskin fibroblasts (*46*). Oral administration of an *n*-hexane extract (160 mg/day) inhibited the binding of ^{3}H-labelled 17β-estradiol to the nuclear estrogen receptors in samples of prostatic tissue from patients with BPH. Binding to the cytosolic and nuclear estrogen and androgen receptors was measured by saturation analysis and an enzyme-linked immunosorbent assay (*47*).

The effect of an *n*-hexane extract of the fruit was evaluated in two human prostatic cell lines, LNCaP and PC3, which are respectively responsive and unre-

sponsive to androgen stimulation. The extract (100 µg/ml) induced proliferation and differentiation in LNCaP cells, but not in PC3 cells, suggesting that the androgen receptor plays a role in mediating the effects of the fruit in LNCaP cells (*48*). In PC3 cells cotransfected with genes for wild-type androgen receptor and a chloramphenicol acetyltransferase reporter under the control of an androgen-responsive element, the extract (25 µg/ml) inhibited androgen-induced chloramphenicol acetyltransferase transcription by 70% (*48*).

n-Hexane, 90% ethanol and supercritical carbon dioxide extracts of the fruit inhibited 5α-reductase activity in vitro (*37*, *43*, *46*, *49–53*). A lipidosterolic extract of the fruit (100 µg/ml) inhibited 5α-reductase activity in the rat ventral prostate by 50%, and reduced conversion of testosterone into dihydrotestosterone in human foreskin fibroblasts by 90%. The conversion of dihydrotestosterone to 5α-androstane-3α-17β-diol by 3α-ketosteroid oxidoreductase was also partially inhibited in cultured human foreskin fibroblasts (*43*). An *n*-hexane extract of the fruit inhibited the activity of both 5α-reductase and 17β-hydroxysteroid dehydrogenase in cultures of epithelial cells (IC_{50} 60 and 40 µg/ml, respectively) and fibroblast cells (IC_{50} 30 and 200 µg/ml, respectively) obtained from the prostates of patients with BPH (*50*). One study reported no effect of several lipidosterolic extracts of the fruit on the activity of 5α-reductase from human prostate or on dihydrotestosterone binding to the rat prostatic androgen receptors at concentrations up to 100 µg/ml (*51*). The reasons for these conflicting results are unclear, and may be due to the different methodologies used. Recently, it has been demonstrated that human 5α-reductase has two isoforms, type 1 and type 2; finasteride, a testosterone 5α-reductase inhibitor has been shown to be a selective inhibitor of the type 2 isoform (inhibitory concentration [K_i] 7.3 nmol/l). Furthermore, an *n*-hexane extract of the fruit was a non-competitive inhibitor of the type 1 isoform (IC_{50} 7.2 µg/ml) and an uncompetitive inhibitor of type 2 (IC_{50} 4.9 µg/ml) (*52*). A 90% ethanol extract of the fruit showed a dose-dependent inhibition of 5α-reductase activity in the epithelium (29% inhibition) and stroma (45% inhibition) of prostate tissue from patients with BPH (*52*). When the extract was fractionated into saponifiable, non-saponifiable and hydrophilic subfractions, only the saponifiable subfraction (consisting mainly of lauric, oleic, myristic and palmitic acids) was active. Of these fatty acids, lauric acid was the most active: it inhibited epithelial and stromal 5α-reductase activity by 51% and 42%, respectively. The inhibition by lauric acid was noncompetitive and dose-dependent up to a concentration of 0.2 mmol/l. The nonsaponifiable fraction, consisting mainly of phytosterols, was weakly active, while the hydrophilic subfractions, containing carbohydrates, amino acids and polysaccharides, were inactive (*53*). A supercritical extract of the fruit inhibited 5α-reductase activity in homogenates of cultured human foreskin fibroblasts (IC_{50} 0.025 mg/ml) (*46*).

One study compared testosterone metabolism in primary cultures of epithelial cells and fibroblasts obtained from the prostates of patients with BPH and prostate cancer. In all cultures, androst-4-ene-3,12-dione, formed by the oxidation of testosterone by 17β-hydroxysteroid dehydrogenase, accounted for 80%

of all metabolites recovered. An *n*-hexane extract of the fruit inhibited the formation of androst-4-ene-3,12-dione in both cell types, indicating that it inhibited the activity of 17β-hydroxysteroid dehydrogenase, unlike finasteride, which was inactive (*50*).

An increase in the activity of 3α-hydroxysteroid-oxidoreductase (the enzyme that metabolizes dihydrotestosterone into the inactive androstenediol form) in prostate tissue from patients with BPH was reported following treatment of patients with an *n*-hexane extract of the fruit (320 mg daily for 3 months). Analysis of enzyme kinetics showed that the V_{max} of 3-hydroxysteroid-oxidoreductase was significantly enhanced in the prostate stroma of treated patients. Since 3-hydroxysteroid-oxidoreductase also has a strong substrate affinity for prostaglandins, increased activity of the enzyme may also increase the metabolism of prostaglandins, thereby accounting for the reduction of prostaglandin-mediated congestion or intraprostatic oedema formation (*54*).

Intragastric administration of an *n*-hexane extract of the fruit to castrated rats for 60–90 days inhibited the increase in total weight of the prostate induced by estradiol and testosterone (*55*). Intragastric administration of a 90% ethanol extract to castrated rats (6 ml/kg body weight, weekly for 8 weeks) inhibited the increase in weight of the ventral prostate, seminal vesicles and coagulation glands induced by testosterone (*37*). Intragastric administration of a 90% ethanol extract of the fruit inhibited prostate growth stimulated by both estradiol and dihydrotestosterone in nude mice into which prostate tissue from humans with BPH had been transplanted (*56*). An *n*-hexane extract of the fruit (30 μg/ml) inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor. Lupenone, hexacosanol and an unsaponified fraction of the extract markedly inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor, but had only a minimal effect on basal cell proliferation (*57*).

Effects on signal transduction

Addition of an *n*-hexane extract of the fruit (1–10 μg/ml) to Chinese hamster ovary cells completely inhibited the effects of prolactin on potassium conductance, protein kinase C activity and intracellular concentrations of calcium. These results suggest that the extract may inhibit prolactin-induced prostatic growth by interfering with the transduction signals involving the prolactin receptor (*58*). Lipidosterolic extracts of the fruit noncompetitively inhibited radioligand binding to human prostatic α_1-adrenoceptors and agonist-induced [^{3}H]inositol phosphate formation (*59*).

Clinical pharmacology

Placebo-controlled clinical trials

Eleven double-blind, placebo-controlled studies have assessed the effects of lipidosterolic extracts of Fructus Serenoae Repentis in the symptomatic treatment of mild to moderate BPH (*26–33*, *60–62*). The number of patients in each study

ranged from 22 to 205, and the dosage of the extract was generally 160 mg twice daily for 1–3 months. All but one study (*61*) reported that the extract was significantly more effective than placebo in reducing the symptoms of mild to moderate BPH. In this study of 70 patients, which was also randomized, although a significant improvement in flow rate was seen in patients treated with either a hexane extract of the fruit (320 mg) or placebo daily for 3 months, no significant difference between the treatment groups was observed (*61*). However, most studies demonstrated an increase in urinary flow rate and a decrease in postvoid residual urine volume (*26*). In another study which was also randomized, 205 patients were treated with 320 mg extract or placebo daily for 3 months. The study concluded that the extract was superior to placebo in reducing the total symptom score (polyuria, nocturia, dysuria, and urgency and hesitancy of micturition), improving the quality of life score, and increasing urinary volume (*62*).

A study was performed on 176 patients with BPH who had been unresponsive to placebo treatment in previous clinical studies. After 30 days of treatment with an extract of the fruit (160 mg, twice daily), there was a significant reduction in dysuria, polyuria and nocturia in the treated group as compared with the placebo group. Patients treated with the extract had a significantly greater increase in mean peak urinary flow rate (28.9%), as compared with those that received the placebo (8.5%), and the overall efficacy of the extract was rated higher than that of the placebo by both patients and physicians (*33*).

Another double-blind, placebo-controlled study assessed the effect of a lipidosterolic extract in the reduction of prostate oedema and congestion in 18 patients with BPH. Histopathological analysis of enucleated prostate tissue from patients treated preoperatively with the extract (320 mg daily for 12 weeks) showed a significant decrease in prostate stromal oedema and congestion in treated patients, as compared with those in the placebo group ($P \leqslant 0.05$) (*63*).

Controlled clinical trials

In a controlled clinical trial, 25 men with symptoms of urinary obstruction were randomized into two groups: 15 patients received no treatment, while 10 were treated with an *n*-hexane extract of Fructus Serenoae Repentis (320 mg extract daily). After 3 months, prostatic specimens were removed by suprapubic prostatectomy and were sectioned into three regions (i.e. periurethral, subcapsular and intermediate). In each region, the concentration of testosterone, dihydrotestosterone and epidermal growth factor was measured by radioimmunoassay. In the patients treated with the extract, a significant reduction ($P < 0.001$) in the concentration of dihydrotestosterone (50%) and epidermal growth factor (50%), and a significant increase ($P < 0.001$) in testosterone levels (125%), were observed in the periurethral region (*64*).

Clinical trials without controls

Numerous clinical studies without controls of men with BPH have reported improvements in both objective and subjective variables after treatment with lipidosterolic extracts of the fruit (*15–28*). The largest trial of 1334 patients treated with 320 mg of a lipidosterolic fruit extract daily for 6 months showed an improvement in postvoid residual urine volume (50% decrease), nocturia (54% decrease) and polyuria (37% decrease) (*16*). The results of a prospective multicentre study in which 435 patients with BPH were treated with a lipidosterolic extract of the fruit (320 mg daily for 3 years) showed a steady improvement in micturition. The improvement was due to a marked decrease in symptoms and postvoid residual urine volume (50% decrease), and an increase in peak urinary flow rate (about 25%) (*17*). Another multicentre study analysed the effect of a lipidosterolic extract of the fruit (160 mg twice daily for 3 months) in 305 patients with mild to moderate BPH. After treatment, increases in maximal and mean urinary flow rates (of 25% and 27%, respectively) and a 35% improvement in the mean International Prostate Symptom Score were seen (*18*). Other studies have also reported improvements in symptoms and objective measurements of disease severity after 1–6 months of treatment with a lipidosterolic extract of the fruit (320 mg daily) (*19–28*). Generally, studies involving periodic evaluation over the course of treatment have demonstrated that improvements in both objective and subjective variables were progressive over time (*17*, *24–27*).

Comparative trials

An *n*-hexane extract of Fructus Serenoae Repentis, finasteride and α_1-receptor antagonists have been shown to be clinically effective in the treatment of BPH in comparative trials (*16*, *65–69*). One large international randomized, double-blind clinical trial compared the efficacy of the extract (320 mg daily) with that of finasteride (5 mg daily) in the treatment of 1098 patients with mild to moderate BPH. After 6 months of therapy, the International Prostate Symptom Score decreased from baseline by 37% in patients treated with the extract as compared with a decrease of 39% in patients who received finasteride. No significant difference was observed between the treatment groups in improvement of patient-rated quality of life scores and the primary end-point of objective symptom score. Both treatments resulted in improved peak urinary flow rates and a reduction in the size of the prostate. Peak urinary flow rate increased from 10.6 ml/s to 13.3 ml/s in patients treated with the extract, and from 10.8 ml/s to 14.0 ml/s in those who received finasteride. The size of the prostate was reduced by 6% in patients treated with the extract, and by 18% in those treated with finasteride. Serum prostate-specific antigen levels were reduced by 41% following finasteride treatment, but remained unchanged in patients treated with the extract (*16*).

Other smaller, shorter, randomized double-blind trials involving groups of 41–63 patients compared the efficacy of the fruit extract (320 mg daily) with the α_1-receptor antagonists alfuzosin and prazosin (*68*, *69*). In a 3-week comparative trial with alfuzosin, the total mean symptom score using Boyarsky's rating scale improved by 27% and 39% in patients treated with the extract and alfuzosin, respectively. Although improvements in the peak urinary flow rates were greater in the alfuzosin-treated group, there was no significant difference between the treatments (*68*). In a 12-week randomized trial comparing the efficacy of a fruit extract (in 20 patients) and prazocin (in 21 patients), improvements in polyuria, mean urinary flow rate and postvoid residual urine volume were similar in both groups, but no statistical analysis of the data was provided by the investigators (*67*). Further large, well-designed, randomized trials of long duration are necessary to compare adequately the clinical efficacy of Fructus Serenoae Repentis and α_1-receptor antagonists.

Four reviews of the randomized controlled clinical trials have indicated that lipidosterolic extracts of the fruit improve the symptoms of urinary tract disorders and urinary flow rates in men with mild to moderate BPH (*14*, *68*–*70*).

Pharmacokinetics

The pharmacokinetics of Fructus Serenoae Repentis were investigated in a bioequivalence study that compared a new capsule formulation (320 mg/capsule) to a reference preparation (160 mg/capsule). Concentrations of the components of the extract were measured in plasma samples from 12 healthy fasting males (mean age 24 years) after oral administration of 320 mg extract (either one capsule of 320 mg or two capsules of 160 mg) (*71*). However, the methodology used in this study was questionable.

Tissue distribution was measured in rats after intragastric administration of a lipidosterolic extract supplemented with radiolabelled oleic acid, lauric acid or β-sitosterol. This investigation demonstrated that the uptake of the extract was much higher in the prostate than either the liver or genitourinary tissues (*72*).

Toxicity

Clinical studies have shown that extracts of Fructus Serenoae Repentis are very well tolerated in humans (*16*, *69*). Minor gastrointestinal side-effects have been reported in most of the clinical trials, but results from standard blood chemistry tests were normal (*69*).

Contraindications

Owing to its effects on androgen and estrogen metabolism, the use of Fructus Serenoae Repentis during pregnancy or lactation and in children under the age of 12 years is contraindicated.

Warnings

Fructus Serenoae Repentis relieves the symptoms associated with BPH, but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or in cases of blood in the urine or acute urinary retention, contact a physician (*1*).

Precautions

Pregnancy: teratogenic effects

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

Pregnancy: non-teratogenic effects

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

Nursing mothers

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during lactation.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

Adverse reactions

Both short- and long-term clinical studies have found that extracts of Fructus Serenoae Repentis are very well tolerated. Occasional nausea, diarrhoea and other minor gastrointestinal complaints have been reported (*18*).

Dosage forms

Crude drug, lipidosterolic extracts (*n*-hexane, 90% ethanol or fluid [carbon dioxide] supercritical extracts standardized to contain 70–95% free fatty acids and corresponding ethyl esters), and preparations thereof. Store in a tightly closed container in a cool, dry place.

Posology

(Unless otherwise indicated)
Daily dosage: 1–2 g crude drug or 320 mg (as a single dose or 160 mg twice daily) of a lipidosterolic extract (*n*-hexane, 90% ethanol or supercritical

fluid [carbon dioxide] extract standardized to contain between 70 and 95% free fatty acids and corresponding ethyl esters) or equivalent preparations (*16–33, 60–62*).

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Fructus Silybi Mariae

Definition

Fructus Silybi Mariae consists of the dried ripe fruits, freed from the pappus, of *Silybum marianum* (L.) Gaertn., Asteraceae (*1*, *2*).

Synonyms

Carduus marianus L., *Carthamus maculatum* Lam., *Cirsium maculatum* Scop., *Mariana mariana* (L) Hill., *Silybum maculatum* Moench. (*3*, *4*). Asteraceae are also known as Compositae.

Selected vernacular names

Akùb, Artichnuat sauvage, blessed thistle, bull thistle, cardo blanco, cardo de burro, cardo mariano, carduo mariano, chardon argente, chardon-marie, épine blanche, Frauendistelfrüchte, fructus cardui mariae, fruit de chardon marie, holy thistle, kharshat barri, khorfeish, kocakavkas, kuub, Lady's milk, Lady's thistle, lait de Notre Dame, marian thistle, máriatövis-termés, mariazami, Mariendistel, Mariendistelfrüchte, Marienkörner, maritighal, mild marian thistle, milk thistle, pternix, shawkeddiman, Silberdistil, silybe, silybon, silybum, St Mary's thistle, thistle, thistle of the Blessed Virgin, true thistle, variegated marian thistle (*3–7*).

Geographical distribution

Indigenous to North Africa, Asia Minor, southern Europe and southern Russian Federation; naturalized in North and South America, Australia, China and Central Europe (*3*, *4*).

Description

An annual or biennial herb, stem 20–150 cm high, green, glabrous or slightly arachnoid-pubescent. Leaves alternate, large, glossy green, white-veined or variegated, glabrous with strongly spiny margins, basal leaves (25–50 cm long, 12–25 cm wide) cauline, pinnatifid. Inflorescence large, composed of red-purple, hermaphrodite, tubular florets gathered into a capitulum (2.5–4.0 cm in diameter), tucked in an involucre with thorny external bracts. Fruits 6–7 mm long, composed of 6–8 hard-skinned achenes with a white, silky pappus (15–20 mm in diameter) at apex. $2n = 34$ (*3*, *7–12*).

Plant material of interest: dried ripe fruits, freed from the pappus

General appearance

Obliquely obovoid with remainder of a flower crown on its top; 6–7 mm long, up to 3 mm wide, 1.5 mm thick. Testa shiny brownish-black or matt greyish-brown, with dark or greyish-white dots. At the tip, there is a projecting yellowish cartilaginous, swollen ring, and at the bottom at the side, a canaliculate hilum. Silvery pappus absent from the drug. Varieties are white, grey and black (*2*, *4*).

Organoleptic properties

Odour: scarcely perceptible; taste: oily, bitter (*2–4*).

Microscopic characteristics

Pericarp epidermis a colourless palisade layer of cells (about 75 µm long and 8 µm wide) with a strongly thickened outside wall, which reduces the lumen in that part of the cell to a slit; subepidermal layer composed of colourless, thin-walled, parenchyma cells or groups of parenchyma cells alternating with a variable number of pigmented cells; innermost layer mostly collapsed and containing cigar-shaped or monoclinic prismatic crystals of calcium oxalate. Testa epidermis consists of large, lemon-yellow, palisade-like, elongated cells (about 150 µm long) with striated walls and narrow lumen widening slightly at the ends; subepidermal layers have lignified and pitted cells (*2*, *4*).

Powdered plant material

Brownish-yellow. Fragments of colourless palisade-like epidermal cells from the fruit wall with attached pigment layer; epidermal cells about 75 µm long and 8 µm wide; cigar-shaped or monoclinic prismatic crystals of calcium oxalate; fragments of lemon-yellow, palisade-like testa cells about 150 µm long; fragments of embryo with thin-walled cells, small druses and lipophilic substances (*2*).

General identity tests

Macroscopic and microscopic examinations (*2*, *4*), and thin-layer chromatography for the presence of marker compounds (taxifolin, silybin, silydianin and silychristin) (*2*, *13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 2% (*1*, *2*).

Total ash

Not more than 8% (*1*, *2*).

Acid-insoluble ash

Not more than 1% (*1*).

Water-soluble extractive

Not less than 10% (*1*).

Loss on drying

Not more than 8% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

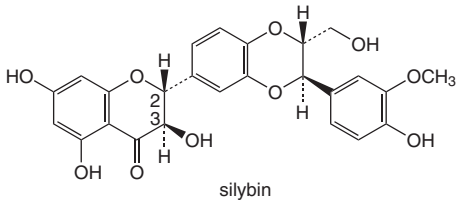
Chemical assays

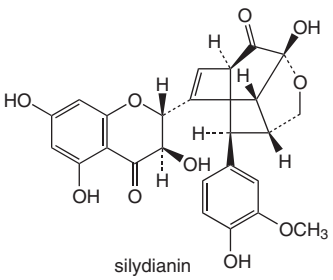
Contains not less than 1.5% silymarin, calculated as silybin, as analysed by high-performance liquid chromatography (*2*). Other high-performance liquid chromatography methods are also available (*3*, *17*, *18*).

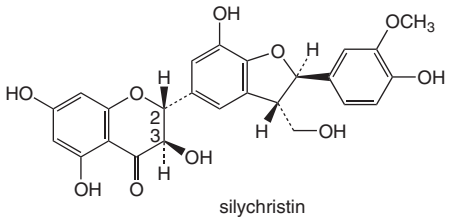
Major chemical constituents

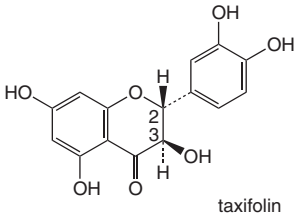
The major active constituents are flavonolignans (1.5–3.0%), collectively known as silymarin. The major components of the silymarin complex are the four

isomers silybin and isosilybin (a 1 : 1 mixture of diastereoisomers), silychristin and silydianin. Other flavonolignans identified include 2,3-dehydrosilybin and 2,3-dehydrosilychristin. Taxifolin, a 2,3-dihydroflavonol, which may be regarded as the parent flavonol of the silymarin compounds, is another major marker for Fructus Silybi Mariae (*3*, *4*, *6–8*, *19*, *20*). The structures of the major silymarin components and taxifolin are presented below.









Medicinal uses

Uses supported by clinical data

Supportive treatment of acute or chronic hepatitis and cirrhosis induced by alcohol, drugs or toxins (*21–34*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of dyspeptic complaints and gallstones (*7*, *35*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, constipation, diabetes, hay fever, uterine haemorrhages and varicose veins (*6*).

Pharmacology

Most of the biochemical and pharmacological studies have been performed using a standardized silymarin preparation, or its major constituent, silybin.

Experimental pharmacology

Antioxidant activity

Silymarin and silybin have antioxidant activity in vitro: both react with oxygen-free radicals such as hydroxyl anions, phenoxy radicals and hypochlorous acid in various model systems such as human platelets, human fibroblasts, rat liver microsomes and mitochondria, and using enzymatically and non-enzymatically generated free inorganic radicals (*36–42*). The production of superoxide anion radicals and nitric oxide was inhibited after treatment of isolated rat Kupffer cells with silybin (IC_{50} 80 µmol/l) (*43*). Both silymarin and silybin inhibited free radical-induced lipid peroxidation in microsomal and mitochondrial preparations of human red blood cells, thereby stabilizing the structure of the cell membrane (*36*, *44–52*). Inhibition of cyclic AMP-dependent phosphodiesterase by silybin, silydianin and silychristin has been demonstrated in vitro. Since cyclic AMP is known to stabilize lysosomal membranes, an increase in the concentration of this nucleoside has been proposed to be the mechanism of membrane stabilization and thus the anti-inflammatory activity of silymarin (*53*). Silybin also inhibits phospholipid synthesis and breakdown in rat liver membranes in vitro, and corrects the alteration in phospholipid metabolism in ethanol-treated rats (*54*). Both silymarin and silybin are incorporated into the hydrophobic–hydrophilic interface of the rat microsomal membrane bilayer and alter the structure by influencing the packing of the acyl chains (*47*).

Antihepatotoxic activity

Silymarin and silybin inhibited hepatotoxicity induced by paracetamol (acetaminophen), amitriptyline, carbon tetrachloride, ethanol, erythromycin estolate, galactosamine, nortriptyline and *tert*-butyl hydroperoxide in rat hepatocytes in vitro (*55–58*). Silybin reduced ischaemic damage to nonparenchymal hepatic cells and improved post-ischaemic function in pig livers (*59*). Allyl alcohol-induced toxicity, and associated lipid peroxidation and glutathione depletion were suppressed after treatment of isolated rat hepatocytes with silymarin and silybin at concentrations of 0.1 and 1.0 mmol/l, respectively (*60*).

Silybin stimulated macromolecular biosynthesis in vitro and in vivo (*61–64*). Silybin increased the rate of ribosomal RNA synthesis by 20% in rat liver, cultured hepatocytes and isolated liver nuclei, via activation of DNA-dependent RNA polymerase I (*63*). Silybin binds to the regulatory subunit of DNA-dependent RNA polymerase I at the estrogen binding site, thereby acting as a natural steroid effector, and thus activating the enzyme and increasing the rate of ribosomal RNA synthesis (*64*). Silybin had no effect on the transcription of RNA polymerase II or III. The increase of ribosomal RNA synthesis in the liver stimulates the formation of mature ribosomes, and hence protein biosynthesis (*63*). Furthermore, an increase in DNA synthesis was observed in livers from hepatectomized rats treated with silybin (27 mg/kg body weight) (*65*).

Intraperitoneal or intragastric administration of silymarin (15–800 mg/kg body weight) to dogs, mice and rats prevented carbon tetrachloride-induced liver damage (*46*, *66–68*). This effect of silymarin was attributed to its antioxidant activity, a decrease in the metabolic activation of carbon tetrachloride, and stabilization of hepatocyte membranes (*46*, *66*, *67*, *69*). Intragastric administration of silymarin (50 mg/kg body weight) improved the metabolism and tissue distribution of aspirin in rats with carbon tetrachloride-induced liver toxicity (*70*). Intraperitoneal administration of either silymarin or silybin markedly inhibited liver damage induced by paracetamol (acetaminophen), *Amanita phalloides* toxins (e.g. phalloidin and α-amanitin), ethanol, galactosamine, halothane, polycyclic aromatic hydrocarbons, rare earth metals (e.g. cerium, praseodymium and lanthanum) and thallium in various rodent models (*50*, *71–81*). Furthermore, intravenous administration of silybin hemisuccinate sodium salt (50 mg/kg body weight) to dogs given sublethal doses of *Amanita phalloides* (85 mg/kg body weight) prevented the increase in concentration of liver enzymes in the blood and the decrease in clotting factors (*82*). The uptake of [^{3}H]dimethyl phalloidin in isolated rat hepatocytes was inhibited by 79% in cells treated with silybin ester (100 µg/ml) (*73*). However, intravenous administration of silybin (50 mg/kg body weight) to rats inhibited the protective effect of ethanol on paracetamol-induced hepatotoxicity. The combination of ethanol and silybin appeared to lead to inhibition of paracetamol metabolism by microsomes (*83*). Intravenous administration of silybin hemisuccinate sodium salt (50 mg/kg body weight) to mice preinfected with sublethal doses of frog virus 3 attenuated histological changes in hepatocyte nuclei; animals treated with a lethal dose of frog virus 3 showed increased survival times (*84–86*).

Intragastric administration of silymarin (50 mg/kg body weight) to rats inhibited collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct occlusion induced by sodium amidotrizoate (*87*). Silymarin increased the redox state and the total glutathione content in the liver, intestine and stomach of rats after intraperitoneal administration (200 mg/kg body weight) (*42*, *88*).

In a transplantation experiment, explanted pig liver was subjected to cold-induced ischaemia by storage of the liver at 4°C for 24 hours, followed by extracorporeal reperfusion for 4 hours. Intravenous administration of 500 mg silybin ester prior to removal of the liver, followed by 400 mg/l during cold storage and 100 mg/h during reperfusion, reduced histological damage to the liver cells (measured by bile production) and improved liver function during reperfusion by 24–66% (measured by bile acid excretion) (*59*).

Anti-inflammatory and anti-allergic activity

Silybin inhibited neutrophil-mediated histamine release induced by *f*-met peptide and anti-IgE from human basophil leukocytes. The inhibitory effect was significantly attenuated ($P < 0.05$) by elevating the extracellular calcium concentration. However, no effect was observed on histamine release induced by the calcium ionophore A23187 (*89*). Silymarin inhibited neutrophil-

mediated histamine release activated by *N*-formylmethionyl-leucyl-phenylalanine from rat peritoneal mast cells at a concentration of 25 µg/ml (*90*). Silybin inhibited the synthesis of leukotriene B_4 (IC_{50} 15 µmol/l) in isolated rat Kupffer cells, but had no effect on prostaglandin E_2 formation at concentrations up to 100 µmol/l (*43*). Silymarin, silybin, silydianin and silychristin inhibited the activity of lipoxygenase and prostaglandin synthetase in vitro (*91–93*). The anti-inflammatory activity of silybin was assessed in human polymorphonuclear leukocytes in vitro. The chemotactic and phagocytic activities of the polymorphonuclear leukocytes were not modified by silybin at concentrations of 0.5–25.0 µg/ml. However, the compound did inhibit luminol-enhanced chemiluminescence, suggesting that the mechanism of anti-inflammatory activity involved the inhibition of hydrogen peroxide formation (*94*). Intragastric administration of silymarin reduced carrageenan-induced footpad oedema in rats (ED_{50} 62.42 mg/kg body weight). Topical application of silymarin inhibited xylene-induced ear inflammation in mice, and its activity was similar to that of indometacin (25 mg/kg body weight). In addition, silymarin inhibited leukocyte accumulation in inflammatory exudates following intraperitoneal administration of carrageenan to mice (*95*).

Intragastric administration (25–1000 mg/kg body weight) of an acetone extract of the fruit containing silybin increased the volume and dry mass of excreted bile in rats (*96*). Intragastric administration of silymarin (100 mg/kg body weight) prevented gastric ulceration in rats induced by cold-restraint and pyloric ligation, but was not effective against ethanol-induced ulcers (*97*). Intragastric administration of silymarin (100 mg/kg body weight) to rats prevented gastric injury induced by ischaemia-reperfusion (*98*).

Clinical pharmacology

Alcohol-induced hepatitis

The efficacy of a standardized silymarin preparation for the treatment of alcohol-induced cirrhosis was assessed in six placebo-controlled clinical trials (*24–27, 31, 33, 99*). The majority of these studies involved between 50 and 100 patients, with one study including 170 patients (*26*). Patients generally received an oral dose of 280–420 mg (140 mg two or three times daily) of a standardized silymarin preparation or placebo. One of the studies had a treatment period of up to 4 years, and used survival rates as their outcome parameter. The results of this study showed a significant decrease in the mortality of patients treated with silymarin as compared with placebo ($P < 0.05$) (*26*). After treatment with the silymarin preparation (140 mg twice daily), a decrease in total bilirubin, liver enzymes and serum N-terminal propeptide of collagen type III levels was observed (*25*). A 6-month trial that was also double-blind assessed the efficacy of silymarin in patients who had histological documentation of chronic alcoholic hepatitis. Silymarin treatment improved histology, and lymphocyte proliferation and lipid peroxidation (*24*). In two studies that were also randomized and double-blind, treatment of 163 patients with the

silymarin preparation decreased serum levels of liver enzymes, improved liver function, and returned sulfobromophthalein levels to normal, as compared with placebo (*27*, *31*). Another trial that was also randomized and double-blind analysed the effects of silymarin in 116 patients with alcohol-induced hepatitis, 58 of whom had liver cirrhosis. Patients received 420 mg silymarin or placebo daily for 3 months. A significant improvement was noted in both groups ($P < 0.05$); however, silymarin was not more effective than placebo (*99*).

Five double-blind clinical trials assessed the efficacy of silymarin in the treatment of various chronic liver diseases induced by alcohol (*22*, *23*, *25*, *29*, *30*). In four of these trials, treatment of patients with 420 mg of the silymarin preparation daily for 6 months decreased the serum levels of bilirubin, procollagen III peptide and liver enzymes, and increased serum glutathione peroxidase activity and lectin-induced lymphoblast transformation (*23*, *25*, *29*, *30*). In the fifth study, which was also placebo-controlled, the efficacy of silymarin was assessed in 20 patients with various chronic liver diseases. After 13 months of treatment (420 mg daily), histopathological findings showed improvements in the treated group as compared with the group that received placebo (*22*).

In a randomized trial of 60 patients with diabetes caused by alcohol-induced cirrhosis, patients received either 600 mg silymarin daily or no treatment for 6 months (*100*). The blood glucose and malondialdehyde levels, daily insulin need and fasting insulinaemia levels were all significantly lower in treated patients than in those that were untreated ($P < 0.05$), and lower than initial baseline values (*100*, *101*). A study without controls assessed the efficacy of a standardized silymarin preparation (420 mg daily) in inhibiting fibrotic activity in 277 patients with various chronic liver diseases. In liver fibrosis, the serum level of the procollagen III peptide increases. The elevated levels of this peptide decreased over the 4-week treatment period (*102*). In a drug monitoring study without controls, 108 patients with alcohol-induced hepatotoxicity and liver inflammation were treated with silymarin (200–400 mg/kg body weight, in a single dose) daily for 5 weeks. After treatment, the serum procollagen III peptide and liver enzyme levels were lower in comparison to the initial baseline values. The preparation was generally well tolerated in 98% of patients (*103*). The safety and efficacy of silymarin were evaluated in over 3500 patients in two drug-monitoring studies. In one study, 2637 patients with various liver disorders were treated with a standardized silymarin preparation (560 mg, given in four divided doses) daily for 8 weeks. Subjective symptoms decreased by 63%, clinical findings improved and elevated serum levels of liver enzymes were reduced in the treated group. Treatment was rated as very good, good or satisfactory by 88% of the physicians (*21*). Minor gastrointestinal side-effects were reported in 1% of patients (*21*, *28*).

Acute and chronic viral hepatitis

Three controlled trials assessed the efficacy of silymarin in the treatment of acute viral hepatitis (*104–106*). In a randomized, double-blind study of 57

patients with acute viral hepatitis A or B, patients received 420 mg of a standardized silymarin preparation or placebo daily for 3 weeks. In the treatment group, 40% of patients had a normalized blood bilirubin level, as compared with 11% of the placebo group; 82% of the treated patients had a normalized blood level of aspartamine transaminase, as compared with 52% of the placebo group. There was no difference between the two groups in the number of patients who developed immunity (*105*). In another trial, the duration of inpatient care was shown to be shorter for patients treated with silymarin, compared to those who received supportive care (23.3 and 30.4 days, respectively). In patients with viral hepatitis B, treatment with silymarin led to a shorter interval to the development of immunity (30.4 days), compared to supportive therapy only (41.2 days) (*104*). A double-blind study in patients with acute viral hepatitis indicated that daily treatment with 420 mg silymarin (three doses of 140 mg) decreased the complications associated with the infection (*106*).

A 12-month study combining two double-blind, placebo-controlled trials assessed the efficacy of silymarin in the treatment of chronic hepatitis, with or without cirrhosis, in 36 patients. Patients were treated with 420 mg of a standardized silymarin preparation or placebo daily for 3–12 months. Assessment of serum levels of bilirubin and liver enzymes did not reveal any significant differences in liver function between the treatment and placebo groups. However, histological improvements were noted in patients who received silymarin (*107*).

Organic compound-induced hepatitis

A controlled clinical study of patients with a 5–20-year history of occupational exposure to toluene and/or xylene vapours was performed to assess the efficacy of a standardized silymarin preparation on liver function. Thirty patients were treated orally with 140 mg of the preparation three times daily for 30 days, and the results were compared with those from 19 untreated matched controls. Both liver function and platelet counts markedly improved in the treated patients (the elevated serum levels of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were reduced, and the low platelet numbers increased) as compared with the controls (*32*). In another study, the effects of a silymarin preparation (420 mg/day) on liver function in 14 patients chronically exposed to the organophosphate malathion were assessed. After treatment, patients showed no improvement in liver function tests when compared with the controls (10 healthy volunteers) (*108*).

Drug-induced hepatitis

A double-blind, placebo-controlled study assessed the efficacy of silymarin in the prevention of hepatic damage induced by psychotropic drugs. Sixty patients receiving chronic therapy with psychotropic drugs (butyrophenones or phenothiazines) were treated orally with 800 mg silymarin or placebo daily for 90 days. Silymarin treatment improved liver function and reduced lipoperoxida-

tive hepatic damage as determined by serum malondialdehyde levels (the end-product of the oxidation of polyunsaturated fatty acids) (*109*). A small clinical study found improvements in biochemical parameters in 19 patients using psychotropic drugs after 6 months of treatment with silymarin (*110*).

Toxin-induced hepatitis

Numerous case reports have indicated that silymarin and silybin are effective in the treatment of poisoning due to ingestion of the deathcap mushroom *Amanita phalloides* (*34*, *111–114*). *Amanita* toxins inhibit the activity of RNA polymerase in hepatocytes, causing cell death after 12–24 hours. In a clinical trial without controls, 60 patients were treated intravenously with silybin (20 mg/kg body weight, daily for 1–2 days), 24–36 hours after ingestion of *Amanita phalloides*. The survival rate was 100% (*34*). Results of a multicentre study of 252 cases of poisoning due to ingestion of *Amanita phalloides* indicated that intravenous infusion of silybin (20 mg/kg body weight, daily for 1–2 days), in combination with the standard management techniques, dramatically reduced mortality, without producing side-effects (*111–113*).

Assessment of the clinical trials of silymarin for the treatment of hepatitis induced by alcohol, drugs or toxins, and acute and chronic viral hepatitis should be interpreted with caution because of the small number of patients involved, the heterogeneity of diagnoses and outcome parameters, and the inconsistent reporting of alcohol intake by patients during the studies (*115*).

Pharmacokinetics

In a randomized, four-way crossover study without controls, a single dose of 102, 153, 203 or 254 mg silybin was administered orally to six healthy males. Silybin and isosilybin concentrations in plasma were measured as unconjugated compounds as well as total isomers after hydrolysis using high-performance liquid chromatography. Areas under the curve were linear with the dose, and only 10% of total silybin in the plasma was in the conjugated form. The elimination half-life of unconjugated silybin was less than 1 hour; that of total silybin was estimated to be 6 hours. Approximately 5% of the dose was excreted into the urine as total silybin, corresponding to a renal clearance rate of 30 ml/min (*116*).

After oral administration of a single dose of 560 mg silymarin (equivalent to 240 mg silybin) to six healthy volunteers, maximum serum concentrations of silybin were low, ranging from 0.18 to 0.62 µg/ml. Only 1–2% of the dose was excreted in the urine during the 24 hours following administration. After oral administration of a single dose of 140 mg silymarin (equivalent to 60 mg silybin) to 14 patients who had undergone cholecystectomy, bile collected from the T-tube drains contained 11–47 µg/ml silybin, equivalent to 7–15% of the dose, after 24 hours (*117*).

Following oral administration of a single dose of a standardized silymarin preparation (140 mg) to nine patients who had undergone cholecystectomy, the urinary and biliary excretion of silybin, silydianin and silychristin were mea-

sured. The urinary excretion of silybin and silychristin was insignificant. Both silybin and silychristin were excreted in the bile in the form of sulfate and glucuronide conjugates. The total elimination of silybin was estimated to be 20–40% and that of silychristin was 4–10%. Urinary excretion of silymarin occurred over a 24-hour period, with maximum excretion occurring between 2 and 9 hours after administration (*118*).

The bioavailability of silymarin varies considerably and is dependent on the formulation of the product (*119*).

Contraindications

Fructus Silybi Mariae is contraindicated in cases of known allergy to plants of the Asteraceae family (*120*).

Warnings

No information available.

Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Fructus Silybi Mariae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Crude drug: one case of anaphylactic shock was reported in a patient ingesting a tea prepared from Fructus Silybi Mariae (*120*). Standardized preparation: a mild laxative effect has been reported (*35*).

Dosage forms

Usually standardized extracts for phytomedicine; crude drug for decoction (*4*). Store in a well-closed container, protected from light and humidity (*2*).

Posology

(Unless otherwise indicated)

Daily dosage: 12–15 g crude drug (*35*); 200–400 mg silymarin, calculated as silybin, in standardized preparations (*35*).

A parenteral preparation, silybin hemisuccinate sodium salt, is available in Germany for treatment of poisoning due to ingestion of *Amanita phalloides* (*111–114, 121*). The total dosage is 20 mg/kg body weight, given as four infusions over a 24-hour period, with each dose administered over a 2-hour period (*121*).

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Herba Tanaceti Parthenii

Definition

Herba Tanaceti Parthenii consists of the dried leaves (*1*), or dried aerial parts of *Tanacetum parthenium* (L.) Schultz Bip. (Asteraceae) (*2*, *3*).

Synonyms

Chrysanthemum parthenium (L.) Bernh., *Leucanthemum parthenium* (L.) Gren & Gordon, *Matricaria eximia* Hort., *M. parthenium* L., *Pyrethrum parthenium* (L.) Sm. (*4–6*). Asteraceae are also known as Compositae.

Selected vernacular names

Acetilla, âghovân, alfinetes de senhora, altamisa, altamisa mexicana, altamza, amargosa, artemijio, artemijo, artmija, bachelor's buttons, boulet, bouton d'argent, camamieri, camomilla, camoumida, camsumilha, canamelha, featherfew, featherfoil, feather-fully, febrifuge plant, feverfew, feverfew tansy, flirtwort, grande camomille, hierba Santa Maria, manzanilla, matricaria, matricaria comum, midsummer daisy, Moederkruid, Mutterkraut, natsushirogiku, Santa Maria, varadika, vettervoo (*3–5*, *7*).

Geographical distribution

Indigenous to south-east Europe, as far east as the Caucasus, but commonly found throughout Europe and the United States of America (*8*, *9*).

Description

A perennial plant up to 30–90 cm high. Stem up to 5 mm in diameter, more or less branched. Leaves greenish-yellow, 2–5 cm, sometimes up to 10 cm, long; pinnatisect to bipinnate, petiolate, alternate, more or less pubescent on both sides. Capitula grouped in wide corymbs of 5–30 florets, each floret with long pedicels, and 1.2–2.2 cm in diameter. Involucre in the shape of a hemisphere, 6–8 mm wide and composed of numerous partly overlapping sheathing bracts; interior bracts narrow, obtuse, scarious and fragmented at apex; exterior bracts oval and membranous on edges. Central hermaphrodite flowers yellow, tubiform, 5-toothed, and have 5 stamens inserted on the corolla; filaments entirely free, but the anthers welded together in a tube, through which passes the style

with its 2 stigmatic branches. Peripheral female flowers have a white 3-toothed ligule 2–7 mm long. Fruit an achene, 1.2–1.5 mm long, brown when mature, with 5–10 white longitudinal ribs; glandular with a short membranous, crenulate crown (*3*, *5*, *7*, *10*).

Plant material of interest: dried leaves or aerial parts

General appearance

Stem bright green, longitudinally furrowed, almost quadrangular, slightly pubescent. Leaves pinnatisect or bipinnate, divided into 5–9 segments of which the lamina is coarsely crenate at edge, apex obtuse, a prominent central vein to the underside, both surfaces pubescent (*1*–*3*).

Organoleptic properties

Odour: camphorous; taste: bitter (*3*).

Microscopic characteristics

Epidermal cells have sinuate walls, striated cuticle and anomocytic stomata, more frequent on the lower epidermis. Trichomes, more abundant on the lower epidermis, of 2 types: covering trichomes uniseriate, consisting of a trapezoidal basal cell with a striated cuticle composed of 3–5 small, rectangular, thick-walled cells, and elongated, tapering apical cells, often curved at 90° to the axis of the basal cell; glandular trichomes slightly sunken, composed of a short, biseriate, 2- or 4-celled stalk and a biseriate head of 4 cells, around which the cuticle forms a bladder-like covering; spherical, echinulate pollen grains about 25 µm in diameter with 3 germinal pores (*1*, *3*).

Powdered plant material

Epidermal cells have sinuate walls and a striated cuticle. Numerous large multicellular, uniseriate trichomes, consisting of a trapezoidal basal cell with a striated cuticle composed of 3–5 small, rectangular, thick-walled cells, and terminated by elongated, tapering apical cells, often curved at 90° to the axis of the basal cell. Secretory hairs sparse, but typical of Asteraceae family. Numerous punctate spiral vessels; stratified parenchyma or collenchyma cells; isolated calcium oxalate crystals in the interior of the mesophyll (*3*).

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography, and high-performance liquid chromatography for the presence of parthenolide (*1*, *3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Foreign organic matter

Not more than 10%, including stems greater than 5 mm in diameter (*1*, *3*).

Total ash

Not more than 12% (*1*, *3*).

Acid-insoluble ash

Not more than 3% (*1*, *2*).

Water-soluble extractive

Not less than 15% (*2*).

Loss on drying

Not more than 10% (*1*, *3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia* (*12*), and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Other purity tests

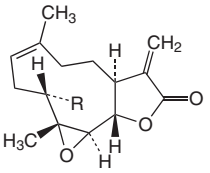
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

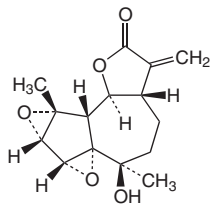
Contains not less than 0.2% parthenolide (dry weight), as determined by high-performance liquid chromatography (*3*).

Major chemical constituents

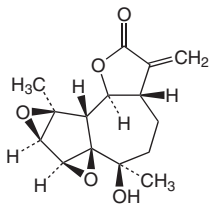
The major constituent is parthenolide (up to 0.9%), a germacranolide sesquiterpene lactone (*14–16*). Parthenolide and other characteristic sesquiterpene lactones, including members of the guaianolides (e.g. canin and artecanin), contain an α-methylenebutyrolactone structure. To date, more than 45 sesquiterpenes have been identified in Herba Tanaceti Parthenii. Monoterpenes, flavonoids and polyacetylenes have also been detected (*1*, *4*, *10*, *12*, *17–19*). The structures of the representative sesquiterpene lactones, parthenolide, 3β-hydroxyparthenolide, canin and artecanin, are presented below.



parthenolide R = H
3β-hydroxyparthenolide R = OH



artecanin



canin

Medicinal uses

Uses supported by clinical data

Prevention of migraine (*20–24*). Although Herba Tanaceti Parthenii has been used for treatment of rheumatoid arthritis, a clinical study failed to prove any beneficial effects (*25*).

Uses described in pharmacopoeias and traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of anaemia, arthritis, asthma, common cold, constipation, diarrhoea, dysmenorrhoea, dyspepsia, oedema, fever, indigestion, insect bites, rheumatism, sciatica, tinnitus, toothache and vertigo (*4*, *26–30*).

Pharmacology

Experimental pharmacology

Prevention and treatment of migraine

The mechanism of action of Herba Tanaceti Parthenii in the prevention of migraine is currently a matter of debate (*27*, *31*, *32*). However, based on

pharmacological studies of the herb and parthenolide, the mechanism appears to be threefold: antiinflammatory activity, an effect on platelets and inhibition of serotonin binding.

Anti-inflammatory activity

Extracts of the herb and parthenolide both inhibit the biosynthesis of prostaglandins, leukotrienes and thromboxanes, collectively known as eicosanoids, which are potent mediators of inflammation. An aqueous extract of the herb (50 µg/ml) inhibited the activity of lipoxygenase in rat leukocytes in vitro, thereby reducing the biosynthesis of prostaglandins and thromboxane B_2 (*33*). A chloroform extract of the leaves (IC_{50} < 50 µg/ml) inhibited the biosynthesis in vitro of leukotriene B_4 and thromboxane B_2 in human and rat leukocytes which had been stimulated by *N*-formyl-methionyl-leucyl-phenylalanine or the calcium ionophore A23187 (*34*). The powdered leaf inhibited arachidonic acid metabolism in *Pseudomonas fluorescens* in vitro (*35*). A buffered aqueous extract of the leaves (pH 7.4) inhibited the activity of phospholipase A_2 in human platelets in vitro (30 µl). Phospholipase A_2 facilitates the release of arachidonic acid (the precursor of the eicosanoids) from the cell membrane (*36*). The extract was also shown to prevent both arachidonic acid release and metabolism in human platelets in vitro (*36*, *37*). A chloroform–methanol extract of the leaves (100 µl) inhibited the release of vitamin B_{12}-binding protein in vitro from human polymorphonuclear leukocytes induced by *N*-formyl-methionyl-leucyl-phenylalanine or sodium arachidonate (*38*). An acetone, chloroform or saline extract of the leaves (IC_{50} 0.79 mg/ml) inhibited oxidative burst in vitro in human polymorphonuclear leukocytes induced by phorbol 12-myristate 13-acetate (*39*, *40*). A chloroform extract of the leaves inhibited histamine release in vitro in rat peritoneal mast cells stimulated by anti-IgE antibodies or the calcium ionophore A23187 (*41*). Parthenolide inhibited gene expression in vitro of cyclooxygenase and the proinflammatory cytokines, tumour necrosis factor-α and interleukin-1, in murine macrophages stimulated by lipopolysaccharide. Parthenolide also suppressed protein tyrosine phosphorylation in these cells, which correlated with its inhibitory effect on the expression of cyclooxygenase and the cytokines (*42*).

Effect on platelets

Another possible mechanism of action of the herb and its constituent sesquiterpene lactones involves the inhibition of platelet aggregation and serotonin release from platelets in response to various chemical stimuli (*27*, *43–45*). Aqueous, chloroform or chloroform–methanol extracts of the leaves (up to 100 µl) inhibited human platelet aggregation in vitro induced by arachidonic acid, collagen or adrenalin (*35*, *36*, *38*, *44*, *46*, *47*). A chloroform extract of the fresh leaves of *Tanaceti parthenium* completely inhibited human platelet aggregation in vitro. After fractionation of the extract, only fractions containing constituents with an α-methylenebutyrolactone functional group were active.

Parthenolide was the most active; canin, tanaparthin-α-peroxide and *cis*-cycloheptane lactone ester were partially active (*48*). Although the exact mechanism by which these compounds affect platelet function is unknown, it has been suggested that their ability to undergo Michael addition with thiol groups may influence their biological activity (*48*). The following evidence supports this hypothesis: addition of cysteine or 2-mercaptoethanol to the crude extract or parthenolide completely suppressed their ability to inhibit platelet aggregation. Furthermore, the inhibitory effects of the extract and parthenolide were both dose- and time-dependent, and treatment of platelets with the extract or parthenolide caused a dramatic reduction in the number of thiol groups (*44*, *45*, *48*). Acetone, chloroform or chloroform–methanol extracts of the leaves (100 µl) inhibited serotonin release in vitro from human platelets and polymorphonuclear leukocytes stimulated by arachidonic acid, adenosine diphosphate, collagen and adrenalin (*38*, *46*, *47*). A chloroform–methanol extract did not, however, inhibit serotonin release from human platelets or polymorphonuclear leukocytes stimulated by the calcium ionophore A23187 (*38*). A 95% ethanol extract of the leaves inhibited serotonin release from bovine platelets in vitro (IC_{50} 1.3–2.9 mg/ml) (*49*). The ability of freeze-dried or air-dried aqueous leaf extracts to inhibit serotonin release from human platelets correlated with the concentration of parthenolide in the extracts (*16*, *32*).

Inhibition of serotonin binding

Current evidence also indicates that serotonin receptor-based mechanisms are involved in the pathophysiology of migraine. In vitro studies have demonstrated that parthenolide displaces radioligand binding from cloned serotonin receptors and from serotonin receptors isolated from rat and rabbit brains, indicating that parthenolide may be a low-affinity antagonist (*50*).

A chloroform extract of the fresh leaves of *Tanacetum parthenium* inhibited the contractile response of isolated rings of rabbit aorta to exogenously applied serotonin-receptor agonists (serotonin, angiotensin, phenylephrine, thromboxane mimetic U48819 or thromboxane A_2) (*51*, *52*). However, a chloroform extract of the dried leaves which did not contain parthenolide or other sesquiterpene lactones was not active (*52*).

Toxicology

An in vitro study demonstrated that an extract of the herb or parthenolide was cytotoxic to human peripheral blood mononuclear cells induced by mitogens and synovial cells stimulated by interleukin-1 (*53*). Parthenolide-induced cytotoxicity was due to the inhibition of thymidine incorporation into DNA (*54*, *55*). Intragastric administration of 100 times the normal daily dose for humans of powdered leaf to rats did not result in loss of appetite or weight (*19*).

Clinical pharmacology

Migraine

Five randomized, double-blind, placebo-controlled studies have assessed the efficacy of various Herba Tanaceti Parthenii products for the prevention of migraine (*21–23*, *56*, *57*). Three of the trials used an encapsulated dried or freeze-dried leaf product (*21–23*), while one study used a 90% ethanol extract of the herb bound to microcrystalline cellulose (*56*). The remaining study was reported only as an abstract and the herb preparation used was not defined (*57*). These five trials were analysed recently by two independent reviewers (*24*). The data were analysed in a predefined, standardized fashion, and each trial was assessed using the Jadad scoring system. Although the data would suggest that the herb was more effective than a placebo in preventing migraine, a firm conclusion could not be reached given the shortcomings of the trials (such as small sample size, poor definition of inclusion criteria and lack of washout period) (*24*).

In the first study, 17 patients who had been treating themselves with the fresh leaves of *Tanacetum parthenium* for 3–4 years for migraine were recruited. Patients were administered an oral dose of 50 mg (concentration of parthenolide was not stated) of a freeze-dried leaf preparation or a placebo daily for 6 months. The average number of migraines in the treatment group was 1.69 over the whole treatment period and 1.50 during the final 3 months of the study, compared with 3.13 and 3.43, respectively, in the placebo group (*21*). Bouts of nausea and vomiting were reported 39 times in the treatment group, compared with 116 occasions in the placebo group. The reduction in frequency of nausea and vomiting was significant ($P < 0.05$) (*20*, *21*).

In the second study, 59 patients with a history of migraine attacks were treated daily with either an encapsulated product containing 70–114 mg leaves (equivalent to 0.545 mg parthenolide) or a placebo, after a 1-month placebo run-in. During this crossover trial, patients received the leaf product for 4 months and then a placebo for 4 months. During the treatment phase, a 24% decrease was reported in the number of migraines in the treatment group as compared with the number in the placebo group. No change in the duration of the migraine or in the proportion of attacks associated with an aura was observed in the treatment group. However, a significant reduction in the number of bouts of nausea and vomiting associated with the migraine was reported ($P < 0.02$). Global assessments of efficacy also demonstrated that the leaf product was significantly superior to the placebo in preventing migraines ($P < 0.0001$) (*22*).

In the third study, 57 patients were divided into two groups for the initial open-label phase. Patients were treated with either a placebo or 100 mg encapsulated leaf preparation (standardized to contain 0.2 mg parthenolide) daily for 60 days. After the open-label phase, a randomized, double-blind, placebo-controlled, crossover study was carried out. Patients were again divided into two groups: 30 patients continued to receive 100 mg leaf preparation and 27 patients received a placebo. After 30 days, the treatments were crossed over (i.e. patients who had

received the placebo were then given the leaf preparation, or vice versa) for a further 30 days. No washout period was allowed between each phase. Results of the open-label phase showed a significant reduction in pain intensity of migraines and symptoms such as vomiting, or sensitivity to light or noise in patients in the treatment group ($P < 0.001$). In the double-blind phase, patients in the treatment group reported a significant decrease in the pain intensity of migraines ($P < 0.01$), while patients in the placebo group noted an increase. Similar results were reported after the crossover. In the double-blind phase, a significant decrease in vomiting ($P < 0.001$) and light- and noise-sensitivity ($P < 0.017$) was observed in the treatment group compared with the placebo group (*23*).

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a 90% ethanol extract of the herb bound to microcrystalline cellulose in the prevention of migraine headache in 44 patients. Diagnosis was carried out using the International Headache Society diagnostic criteria. After an initial 1-month placebo run-in, patients were treated with either 143 mg extract standardized to contain 0.5 mg parthenolide or placebo daily for 4 months, then the treatments were crossed over for a further 4 months (*56*). The average response to the two treatments was the same and the extract did not prevent migraines. Statistical significance was not reported.

A study without controls demonstrated that platelet aggregation in 10 patients who had taken preparations of the herb for 3.5–8.0 years was the same as in a control group of four patients who had stopped taking the herb for at least 6 months prior to being tested (*58*).

Rheumatoid arthritis

A double-blind, placebo-controlled trial assessed the efficacy of the herb for the treatment of rheumatoid arthritis. Forty women with rheumatoid arthritis were treated with either 70–86 mg of an encapsulated leaf product or a placebo daily for 6 weeks. No beneficial effects were observed (*25*).

Contraindications

Herba Tanaceti Parthenii is contraindicated in cases of known allergy to plants of the Asteraceae family, and during pregnancy (*1*, *19*, *28*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No significant differences were observed in the mean frequency of chromosomal aberrations or sister-chromatid exchange in the circulating peripheral lym-

phocytes of 30 patients who had taken Herba Tanaceti Parthenii for 11 months or longer. Urine samples from these patients did not induce a significant increase in the number of revertants in the *Salmonella*/microsome assay with or without metabolic activation (*59*).

Pregnancy: teratogenic effects

See Contraindications. The use of Herba Tanaceti Parthenii during pregnancy is contraindicated due to its uterotonic activity in vivo (*19*, *28*).

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; nursing mothers; or paediatric use. Therefore, Herba Tanaceti Parthenii should not be administered during lactation or to children without medical supervision.

Adverse reactions

Dizziness, heartburn, indigestion, inflammation of the mouth and tongue with swelling of the lips, loss of taste, mouth ulceration, and weight gain have been reported (*19*, *21*, *22*). Mouth ulceration is a systemic reaction to Herba Tanaceti Parthenii and requires discontinuation of the product. Inflammation of the mouth and tongue with swelling of the lips appears to be a local reaction that may be overcome by using encapsulated herb products. Abdominal bloating, heart palpitations, constipation, diarrhoea, flatulence, increased menstrual flow, nausea and skin rashes have also been reported to a lesser degree (*21*, *22*, *56*). Allergic reactions, such as contact dermatitis, have also been reported (*19*). Cross-sensitivity between pollen allergens of other members of the Compositae family, *Parthenium hysterophorus* (American feverfew) and *Ambrosia* species (ragweed), has been reported (*60*).

Dosage forms

Crude drug for decoction; powdered drug or extracts in capsules, tablets, tinctures and drops (*2*). Store in a well-closed container, protected from light and humidity (*3*).

Posology

(Unless otherwise indicated)
Daily dosage: encapsulated crude drug equivalent to 0.2–0.6 mg parthenolide (as a chemical marker) for prevention of migraine (*21–23*, *27*, *32*).

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Radix Urticae

Definition

Radix Urticae consists of the dried roots and rhizomes of *Urtica dioica* L., *U. urens* L. (Urticaceae), their hybrids or mixtures thereof (*1*, *2*).

Synonyms

Urtica dioica L.

Urtica gracilis Ait., *U. major* Kanitz., *U. urens maxima* Blackw. (*3*, *4*).

Urtica urens L.

Urtica minor Fuchs, *U. minor* Moench., *U. urens minima* Dod. (*3*, *4*).

Selected vernacular names

Urtica dioica L.

Brennesselwurzel, common nettle, csalángyökér, gazaneh, grande ortie, greater nettle, grosse Brennessel, Haarnesselwurzel, Hanfnesselwurzel, hhurrayq, Nesselwurzel, nettle root, ortica, ortie, ortiga, pokrzywa, qurrays, racine d'ortie, raiz de ortiga, stinging nettle, tsuknida, zwyczajna (*4–6*).

Urtica urens L.

Dwarf nettle, Eiternessel, kleine Brennessel, lesser nettle, ortica minore, ortica piccola, ortie brulante, petite ortie, sha'reláguz, small nettle (*4*, *6–9*).

Geographical distribution

Urtica dioica is indigenous to Africa and western Asia, but is now found in all temperate regions of the world in Africa, North and South America, Asia, Australia and Europe (*3*, *4*, *6*, *7*, *10*).

Owing to the difficulty in botanical differentiation between *Urtica dioica* and *U. urens* in the wild, they are often harvested together. Although both species have a similar distribution, *U. urens* has become less widely distributed due to the reduction of its habitat (*3*).

Description

Urtica dioica L.

A herbaceous perennial with erect, green to purplish square stems, 30–150 cm high, with creeping roots; whole plant covered with stinging hairs. Leaves opposite, cordate at the base, oblong or ovate, finely toothed; upper surface dark green and underside paler. Flowers incomplete, small, green, dioecious (plant has either male or female flowers in separate inflorescences) and occur as racemes in axils of upper leaves; male or barren flowers have a perianth of 4 segments and 4 stamens, which are bent inwards at bud stage; female or fertile flowers have similar perianth surrounding a single 1-seeded carpel, bearing 1 style with a brush-like stigma. Fruit an achene (*3*, *8*).

Urtica urens L.

A herbaceous annual resembling *Urtica dioica*, but is smaller (usually up to 30 cm high), has smaller leaves and flowers are in short, mostly unbranched clusters; male and female flowers appear together in the same raceme. Glabrous except for the stinging hairs (*8*, *11*).

Plant material of interest: dried roots and rhizomes

General appearance

Rhizome cylindrical and tapering, occasionally branched, up to about 6 mm thick at upper end; outer surface yellowish-brown; internodes with deep longitudinal furrows, numerous smooth, very thin and wiry roots arising from the nodes; in the outer part, inner surface creamy-white with a central hollow; fracture fibrous and tough.

Root greyish-brown, irregularly twisted, about 5 mm thick, distinct longitudinal furrows; hollow in cross-section, cut surface white; fracture fibrous and tough (*1*, *7*).

Organoleptic properties

Odourless; taste: faintly aromatic, characteristically bitter (*1*).

Microscopic characteristics

Rhizome: thin cork composed of brown, thin-walled cells, a few rows of tangentially elongated cortical parenchyma and a pericyclic region with fairly numerous fibres; fibres usually in small groups, sometimes single; individual fibres greatly elongated with very thick, lignified walls; some cells of pericycle and outer part of the secondary phloem contain fairly large cluster crystals of calcium oxalate. Cambial region distinct and continuous, with narrow radial groups of vascular tissues separated by wide medullary rays; secondary phloem

mainly parenchymatous, whereas secondary xylem dense and completely lignified; medullary rays in secondary xylem show alternating areas of lignified and unlignified cells; lignified cells have moderately thickened walls and numerous simple pits. Pith composed of rounded, unlignified parenchyma.

Root: very thin cork, narrow phelloderm and secondary phloem and xylem with alternating areas of lignified and unlignified parenchyma in the wide medullary rays, as in the rhizome; a strand of primary xylem in the centre with a few small vessels (*1*).

Powdered plant material

Fibrous and pale beige. Fragments of greatly elongated pericyclic fibres, occurring singly or in groups, with thick and lignified walls, xylem vessels with bordered pits, associated with thick-walled fibres with slit-shaped pits; lignified, moderately thick-walled and pitted parenchyma from the medullary rays of xylem; abundant thin-walled parenchymatous cells, some containing large cluster crystals or scattered crystals of calcium oxalate; fragments of brownish cork (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*), and thin-layer chromatography for scopoletin and phytosterols (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign matter

Not more than 2% (*1*).

Total ash

Not more than 8% (*2*).

Acid-insoluble ash

Not more than 3.5% (*1*).

Water-soluble extractive

Not less than 15% (*1*).

Loss on drying

Not more than 12% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*), and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis for heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

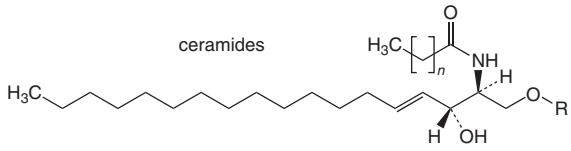
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

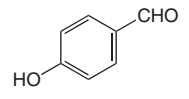
Chemical assays

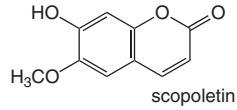
In addition to thin-layer chromatography for qualitative analysis (*2*), enzyme-linked immunosorbent assay and high-performance liquid chromatography methods have also been developed to determine the concentration of *Urtica dioica* agglutinin in Radix Urticae (*15*, *16*). However, concentration limits need to be established.

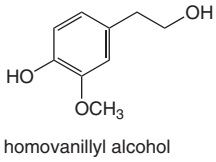
Major chemical constituents

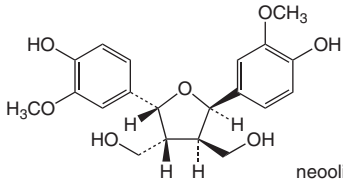
A large number of compounds of different polarity and belonging to various chemical classes, including fatty acids, terpenes, phenylpropanes, lignans, coumarins, triterpenes, ceramides, sterols and lectins, have been isolated from Radix Urticae. Among these are oxalic acid, linoleic acid, 14-octacosanol, 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid, α-dimorphecolic acid (9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid), scopoletin, *p*-hydroxybenzaldehyde, homovanillyl alcohol, β-sitosterol, stigmasterol, 24-*R*-ethyl-5α-cholestan-3β,6α-diol, campesterol, daucosterol (and related glycosides), secoisolariciresinol-9-*O*-β-D-glucoside, neoolivil, oleanolic acid, ursolic acid, *Urtica dioica* agglutinin and polysaccharides RP1–RP5 (*3–5*, *10*, *17–21*). The structures of the representative constituents are presented below.

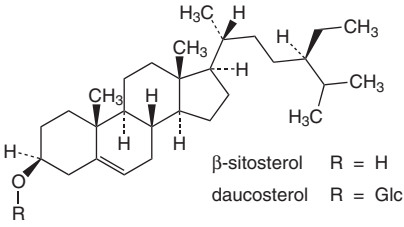


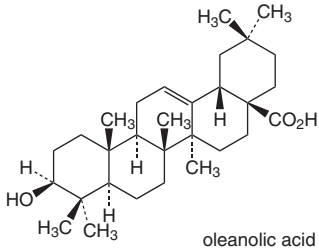












Medicinal uses

Uses supported by clinical data

Symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, urinary retention) resulting from BPH stages I and II, as defined by Alken, in cases where diagnosis of prostate cancer is negative (*22–35*).

Uses described in pharmacopoeias and traditional systems of medicine

As a diuretic and for the treatment of rheumatism and sciatica (*6*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, coughs, dandruff, diabetes, diarrhoea, eczema, fever, gout, haemorrhoids, nose bleeds, scurvy, snakebites and tuberculosis (*5*, *6*). The

plant has also been used to stop uterine bleeding after childbirth, increase lactation and promote hair growth, and as a vermifuge (*5*, *6*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

An ethanol extract of Radix Urticae inhibited the activity of human leukocyte elastase and reduced the amount of the enzyme released by activated polymorphonuclear granulocytes during the inflammatory response. The extract also inhibited degradation of a peptide substrate in vitro by human leukocyte elastase (IC_{50} 3.6 μg/ml) and bovine elastin (IC_{50} 68 μg/ml) (*36*). Intragastric administration of a polysaccharide fraction isolated from Radix Urticae to rats (40 mg/kg body weight) suppressed carrageenan-induced footpad oedema for up to 20 h (*21*, *37*). The activity of the polysaccharides was comparable to that of indometacin (10 mg/kg body weight) (*21*, *37*).

Lymphocyte proliferation

A lyophilized aqueous extract (10 μg/ml) and a 40% alcohol extract of the roots (100 μg/ml) stimulated human lymphocyte proliferation in vitro by 63% and 100%, respectively (*21*, *37*). Polysaccharides isolated from an aqueous root extract induced human lymphocyte proliferation in vitro (10–100 μg/ml) (*21*, *37*). An ethyl acetate extract of the roots induced cell differentiation in human promyelocytic leukaemia HL-60 cells in vitro (ED_{50} 4 μg/ml) (*38*). *Urtica dioica* agglutinin (500 ng/ml), however, inhibited lymphocyte proliferation and the binding of epidermal growth factor to its receptor on A431 epidermoid cancer cells in vitro (*39*). The lectin also exhibited immunomodulatory effects on T-lymphocytes in a dose-dependent manner (*21*, *37*). *Urtica dioica* agglutinin bound to the cell membrane of prostatic hyperplastic cells (*40*) and inhibited their proliferation (*21*).

Effect on benign prostatic hyperplasia

Effect on sex hormone-binding globulin

Sex hormone-binding globulin (SHBG) is a blood plasma protein that binds to circulating androgens and estrogens, thereby regulating their free concentration in plasma. The plasma membrane of the human prostate contains specific SHBG receptors, and SHBG appears to play a role in the development of BPH. A 10% hydroalcoholic extract of the root reduced the binding capacity of SHBG (isolated from human plasma) for 5α-dihydrotestosterone by 67% in vitro (*41*). An aqueous extract of the root (0.6–10.0 mg/ml) inhibited the binding of ^{125}I-labelled SHBG to human prostate membranes in vitro (*42*). The lignan, secoisolariciresinol, and a mixture of the isomeric compounds 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid and 9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from a methanol root extract, reduced the binding of SHBG to 5α-

dihydrotestosterone (*18*). Secoisolariciresinol and its main intestinal transformation products, (–)-3,4-divanillyltetrahydrofuran and enterofuran, displaced the binding of 5α-dihydrotestosterone to SHBG in vitro by 60%, 95% and 73%, respectively (*43*).

Enzymatic activity

Intragastric administration of a 30% ethanol extract of the root to male mice inhibited the activities of 5α-reductase and aromatase (ED_{50} 14.7 and 3.58 mg/ml, respectively) (*44*). However, a hydroalcoholic extract of the root dissolved in dimethyl sulfoxide did not inhibit the activity of 5α-reductase from human prostate cells in vitro (up to 500 µg/ml) (*45*). A standardized hydroalcoholic extract of the roots (IC_{50} 338 µg/ml) inhibited aromatase activity in vitro. A heptane-soluble fraction of the extract was the most effective inhibitor (IC_{50} 9 µg/ml) (*36*). Both ursolic acid and 14-octacosanol isolated from a methanol extract of the roots inhibited the activity of aromatase in vitro (*46*). 9-Hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from the roots inhibited the activity of aromatase in vitro (*19*). Butanol, ether, ethyl acetate and hexane extracts of the roots inhibited the activity of sodium- and potassium-adenosine triphosphatase isolated from prostatic hyperplastic cells by 27.6–81.5% (*47*). In addition, steroidal components of the roots, stigmast-4-en-3-one, stigmasterol and campesterol (1 µmol/l to 1 mmol/l), inhibited sodium- and potassium-adenosine triphosphatase activity by 23–67% (*47*).

Effect on prostate growth

Intragastric administration of a hexane extract of the roots (1.28 g daily) to castrated rats did not inhibit prostate growth stimulated by testosterone or dihydrotestosterone (*45*). Intraperitoneal administration of a hydroalcoholic extract of the roots (20 mg/kg body weight) suppressed testosterone-stimulated increases in prostate weight and prostatic ornithine decarboxylase activity in castrated rats (*48*). Daily oral administration of a hydroalcoholic extract of the root to dogs with BPH (30 mg/kg body weight) decreased prostate volume by 30% after 100 days of treatment (*49*).

The effect of various root extracts was assessed after implantation of the fetal urogenital sinus into the prostate gland of adult mice. Intragastric administration of a butanol, cyclohexane or ethyl acetate extract of the root (0.25 ml/daily for 3 weeks) had no effect on the development of BPH in mice. However, intragastric administration of the same dose of a 20% methanol extract of the root reduced the development of BPH by 51.4% (*50*).

Toxicology

The LD_{50} of an aqueous extract or infusion of the roots after intravenous administration to rats was 1721 mg/kg body weight and 1929 mg/kg body weight,

respectively. Oral administration of an infusion of the roots to rats was well tolerated at doses up to 1310 mg/kg body weight (*3*).

Clinical pharmacology

Benign prostatic hyperplasia

Placebo-controlled clinical trials

Three double-blind, placebo-controlled clinical trials have assessed the efficacy of oral administration of Radix Urticae for the symptomatic treatment of lower urinary tract disorders resulting from BPH (*24*, *27*, *35*). One study assessed the efficacy of a 20% methanol extract of the roots in 50 men with BPH stages I and II (*35*). A significant increase in urine volume (by 43.7%; $P = 0.027$) and a significant decrease in serum levels of SHBG ($P = 0.0005$) was observed in patients treated with 600 mg extract daily for 9 weeks. A modest increase in maximum urinary flow of 8% was also observed in the treated group; however, it was not significant (*35*). Another study assessed the efficacy of a 20% methanol extract in 40 men with BPH. Treatment with 1200 mg extract daily for 6 weeks decreased the frequency of micturition and serum levels of SHBG (*27*). The third study assessed the efficacy of a methanol extract in the treatment of 32 men with BPH stage I (*24*). A 4–14% increase in average urinary flow and a 40–53% decrease in postvoid residual volume were observed in patients treated with 600 mg extract daily for 4–6 weeks (*24*).

Clinical trials without controls

Numerous clinical trials without controls have assessed the efficacy of oral administration of various Radix Urticae extracts (20% methanol or 30–45% ethanol) for the symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, dysuria, urine retention) resulting from BPH (*22*, *23*, *25*, *26*, *28–32*, *34*, *51*, *52*). One trial assessed the efficacy of a 40% ethanol extract of the roots in 67 men with BPH. Treatment with 5 ml daily for 6 months decreased nocturia and postvoid residual volume, but did not reduce prostate enlargement (*23*). In another trial, a 20% methanol extract of the roots was assessed in 89 men with BPH. Treatment with 600 mg daily decreased the postvoid residual volume in 75% of patients after 3–24 months (*25*). In a study of 26 men with BPH stage I or II, a decrease in prostate volume was observed in 54% of patients, and a decrease in postvoid residual volume was observed in 75% of patients, after treatment with 1200 mg methanol extract daily for 3–24 weeks (*26*). Ten men with BPH were treated with 30–150 drops of a 45% ethanol extract of the root daily for 30 days. After treatment, the postvoid residual volume decreased by 66% (*29*). In a study of 39 men with BPH stages I–III, an improvement in urinary flow, and a reduction in postvoid residual volume, nocturia and polyuria were seen in 95% of patients after 6 months of treatment with a 20% methanol extract (600–1200 mg daily) (*51*). Twenty-seven men with BPH stages I and II were treated with a 20% methanol extract of the roots for 3.5 months. Postvoid residual volume decreased significantly in 75%

of patients ($P < 0.001$), and maximum urinary flow increased significantly in 50% of patients ($P < 0.002$) (*52*).

Three large-scale multicentre studies involving 14033 men with BPH assessed the efficacy of a 20% methanol extract (*28*, *31*, *32*). In one study, a decrease in nocturia and polyuria was seen in 91% of patients after 6 months of treatment (*28*). In another study, a 50% decrease in nocturia was observed in patients treated with 1200 mg extract daily for 10 weeks (*31*). In the third study, significant improvements in both urinary flow and postvoid residual volume were observed in 4480 patients treated with 600–1200 mg extract daily for 20 weeks ($P < 0.01$) (*32*).

Effects on prostate morphology

Three studies without controls examined the effect of various methanol extracts of Radix Urticae on prostate morphology. Prostate cells were obtained from patients with BPH by needle biopsy, and were analysed for morphological changes before and after treatment. In two of the studies, cells were taken from the patients at various intervals during treatment (*53*, *54*). In the third study, cells were obtained once from the patients, and treatment with the extract was carried out in vitro (*55*). In the first study, 31 men with BPH stages I and II were treated orally with 1200 mg of a 20% methanol root extract daily for 20 weeks. Prostate cells were analysed every 4 weeks by fluorescent microscopy. After 4–16 weeks of treatment, an increase in nuclear volume, as well as hydropic swelling and vacuolization of the cytoplasm, were observed (*53*). In the second study, prostate cells from four men with BPH stage I were examined by electron microscopy. After 6 months of oral treatment with a 20% methanol extract (1200 mg daily), a reduction in the activity of smooth muscle cells and an increase in the secretory activity of glandular epithelial cells were observed (*54*). In the third study, prostate glandular epithelial cells from 33 patients with BPH were analysed by fluorescent microscopy following incubation of the cells in vitro with a 20% methanol extract of the root. Treatment with the extract caused an increase in nuclear volume, loosening of chromatin and hydropic swelling of the cytoplasm. In addition, the number of homogeneous secretory granules was reduced, indicating a reduction in the biological activity of these cells (*55*).

Contraindications

Radix Urticae is contraindicated in cases of known allergy to plants of the Urticaceae family. Owing to its effects on androgen and estrogen metabolism, the use of Radix Urticae during pregnancy and lactation and in children under the age of 12 years is contraindicated.

Warnings

Radix Urticae relieves the symptoms associated with BPH but does not have an effect on the size of the prostate. If symptoms worsen or do not

improve, or in cases of blood in the urine or acute urinary retention, contact a physician.

Precautions

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

Adverse reactions

Clinical studies have shown that extracts of Radix Urticae are well tolerated in humans. A few cases of minor transient gastrointestinal side-effects, such as diarrhoea, gastric pain and nausea (*32*, *35*), and allergic skin reactions (*32*), have been reported.

Dosage forms

Crude drug for infusion; hydroalcoholic extracts (*4*, *56*). Store in a well-closed container, protected from light and humidity (*2*, *13*).

Posology

(Unless otherwise indicated)
Daily dosage: 4–6 g crude drug or equivalent preparations as an infusion (*4*, *56*); 600–1200 mg dried 20% methanol extract (5 : 1) (*22*, *25*, *27*, *31*, *32*); 1.5–7.5 ml 45% ethanol extract (1 : 1) (*29*); 5 ml 40% ethanol extract (1 : 5) (*17*, *23*).

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Folium Uvae Ursi

Definition

Folium Uvae Ursi consists of the dried leaves of *Arctostaphylos uva-ursi* (L.) Spreng. (Ericaceae) (*1–3*).

Synonyms

Arbutus uva-ursi L., *Arctostaphylos media* Greene, *Arctostaphylos officinalis* Wimm., *Arctostaphylos procumbens* Patzke, *Mairania uva-ursi* Desv., *Uva-ursi buxifolia* S.F. Gray, *Uva-ursi procumbens* Moench. (*4*).

Selected vernacular names

Achelblätter, Achelkraut, arberry, arctostaphylos, Bärenkraut, Bärentraube, Bärentraubenblätter, bearberry, bear's grape, Beredruif, berry leaves, brockberry, busserole, coralillo, crowberry, dogberry, enab edhdhib, feuille de busserole, feuille de raisin d'ours, folia artostaphyli, folia garjubae, folia uvae-ursi, folia vaccinii ursi, foxberry, gayuba, herba garjubae, hog cranberry, hojas de gayuba, kinnikinnick, leesikas, lisc maçznicy, mealyberry, medveszölölevel, Moosbeerenblätter, mountain box, ptarmigan berry, raisin d'ours, red bearberry, sagochomi, Sandblätter, Steinbeerenblätter, upland cranberry, uva ursi, uvaursina, uwaurushi, Wolfsbeerenblätter (*4–6*).

Geographical distribution

Found in North America, Asia and northern Europe (*6*).

Description

Procumbent evergreen shrub with trailing stems bearing short ascending branches; branches bear leaves that are ovate, ovate-spatulate to spatulate. Flowers bell-shaped, pinkish-white, hypogynous and borne in small clusters at ends of branches; each flower consists of a calyx of 5 reddish sepals, a reddish-white urceolate corolla, gamopetalous but divided at the margin into 5 short reflexed segments, 10 short stamens with 2-lobed anthers, and syncarpous pistil of 5 carpels. Style portion of the pistil simple, longer than the stamens and ends in a knob-like stigma (*6*).

Plant material of interest: dried leaves

General appearance

Leaf entire or nearly entire; lamina obovate, oblong or spatulate, 7–30 mm long and 5–13 mm wide, apex obtuse or rounded, margin entire or slightly revolute, base cuneate, tapering to a short (about 5 mm long), slightly pubescent petiole. Upper surface green to brownish-green, waxy, shiny and coriaceous, finely wrinkled due to depression of midrib and veins. Lower surface greyish-green, reticulate. Young leaves ciliate on the margins, old leaves glabrous (*1*, *3*, *6*).

Organoleptic properties

Odour: slightly aromatic, tea-like; taste: astringent, bitter (*1*, *6*).

Microscopic characteristics

Both epidermises covered with a thick cuticle; cells of the upper epidermis rectangular with straight, slightly thickened and distinctly pitted and beaded walls; cells of the lower epidermis similar but smaller; numerous large, anomocytic stomata in lower epidermis only. Occasional unicellular, thick-walled, conical trichomes on petiole and margin of young leaves; palisade usually of 3 layers, occasionally more; some spongy mesophyll cells filled with orange-brown pigment; prismatic crystals of calcium oxalate in parenchymatous cells surrounding the narrow, lignified sclerenchymatous fibres associated with the veins (*1*).

Powdered plant material

Greenish-grey or yellowish-green. Numerous cells of the mesophyll with chloroplasts and frequently irregular masses of carbohydrate; fragments of fibrovascular bundles showing spiral tracheae and narrow lignified sclerenchyma fibres associated with crystal fibres containing monoclinic prismatic crystals of calcium oxalate up to 30 µm in length; epidermis with polygonal cells and broadly elliptical anomocytic stomata up to 40 µm in length, surrounded by 5–11 subsidiary cells; pericyclic fibres lignified, of irregular shape with thick, porous, tuberculated walls and curved ends; trichomes unicellular, non-glandular, short, serpentine or straight; numerous fragments of cells containing yellowish-brown resin which turns blueish-black with iron (III) chloride test solution (*3*, *6*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of arbutin, hydroquinone and gallic acid (*2*, *3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

Foreign organic matter

Not more than 5% twigs and not more than 3% other foreign matter (*2*, *3*).

Total ash

Not more than 5% (*2*, *3*).

Acid-insoluble ash

Not more than 1.5% (*2*).

Water-soluble extractive

Not less than 25% (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*8*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*7*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

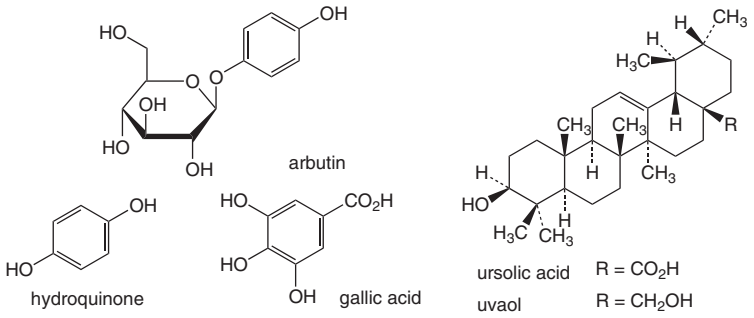
Chemical assays

Contains not less than 7% hydroquinone derivatives calculated as anhydrous arbutin, according to *The Japanese pharmacopoeia* (*2*). Contains not less than 8%

hydroquinone derivatives calculated as anhydrous arbutin, according to the *European pharmacopoeia* (*3*). Quantitative analysis is performed by spectrophotometry at 455 nm (*3*) or by high-performance liquid chromatography for the quantitative analysis of arbutin (*2*), hydroquinone and related derivatives (*9*).

Major chemical constituents

The major constituent is arbutin (5–15%). Related hydroquinone derivatives present include hydroquinone and methylarbutin (up to 4%). Gallic acid is the major phenolic carboxylic acid present, together with galloyl arbutin and up to 20% of gallotannins, flavonoids and triterpenes, mainly ursolic acid and uvaol (*4*, *10*–*12*). The structures of the major constituents are presented below.



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Internally, as a mild urinary antiseptic for moderate inflammatory conditions of the urinary tract and bladder, such as cystitis, urethritis and dysuria (*11*, *13*, *14*).

Uses described in folk medicine, not supported by experimental or clinical data

As a diuretic, to stimulate uterine contractions, and to treat diabetes, poor eyesight, renal or urinary calculi, rheumatism and venereal disease (*4*, *5*, *15*). Topical applications have been used for skin depigmentation (*15*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A 30% ethanol extract of Folium Uvae Ursi inhibited the growth in vitro of *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens* and *Staphylococcus aureus* (*16*). However, 95% ethanol or chloroform extracts had no antibacterial activity (*17, 18*). An aqueous extract of the leaves inhibited the growth of *Streptococcus mutans* OMZ176 in vitro (*19*). Ethanol and ethyl acetate extracts of the leaves were active in vitro against *Escherichia coli, Proteus vulgaris, Streptococcus faecalis* and *Enterobacter aerogenes* (*20*). Arbutin is responsible for most of the antibacterial activity (*21*). Arbutin and hydroquinone inhibited the growth in vitro of *Ureaplasma urealyticum* and *Mycoplasma hominis* (*22*). After ingestion of the leaves, arbutin is absorbed from the gastrointestinal tract, and is hydrolysed by intestinal flora to form the aglycone, hydroquinone (*23*). Hydroquinone is metabolized to glucuronate and sulfate esters that are excreted in the urine (*24, 25*). These active hydroquinone derivatives exert an antiseptic and astringent effect on the urinary mucous membranes when the urine is alkaline (pH 8.0). Their antibacterial action reaches a maximum approximately 3–4 hours after ingestion (*13*).

An aqueous extract of the leaves had antiviral activity in vitro against herpes simplex virus type 2, influenza virus A2 (Mannheim 57) and vaccinia virus at a concentration of 10% (*26*).

Anti-inflammatory activity

Intragastric administration of a 50% methanol extract of the leaves (100 mg/kg body weight) to mice inhibited picryl chloride-induced ear inflammation (*27*). The extract also potentiated the efficacy of prednisolone and dexamethasone in mice (*27, 28*). Arbutin, however, had no effect on the activity of the two steroids (*28*).

Effect on glucose levels

Administration of the leaves (6.35% of diet) to streptozocin-treated mice for 18 days did not reduce plasma glucose levels (*29*).

Effect on calcium excretion

Addition of an infusion of the leaves to the drinking-water (3 g/l) of rats fed a standard diet fortified with calcium (8 g/kg body weight) had no effect on urinary calcium excretion and diuresis (*30*).

Antitussive activity

Arbutin (50–100 mg/kg body weight, administered intraperitoneally or intragastrically) was as active as codeine (10 mg/kg body weight, administered

intraperitoneally) as an antitussive in unanaesthetized cats with coughs induced by nylon fibres (*31*).

Effect on skin depigmentation

Extracts of the leaves have been widely used in cosmetic preparations to lighten the skin, with the active principles being hydroquinone and its derivatives (*15*).

Toxicity and overdose

The oral LD_{50} of hydroquinone ranged from 300 to 1300 mg/kg body weight in rodents and dogs, but was only 42–86 mg/kg body weight in cats. Acute exposure of rats to high doses of hydroquinone (over 1300 mg/kg body weight) caused severe effects on the central nervous system, including hyperexcitability, tremor, convulsions, coma and death (*32*).

Clinical pharmacology

Antibacterial activity

In a study without controls, urine samples from healthy volunteers were collected 3 hours after oral administration of 0.1 or 1.0 g arbutin. The urine samples (adjusted to pH 8.0) and 20 antibacterial compounds (at their usual urine concentration) were tested in vitro using 74 strains of bacteria, including *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Only arbutin (present in urine samples collected after administration of 1.0 g arbutin), gentamicin and nalidixic acid were active against all the strains tested (*24*). Oral administration of 800 mg arbutin or an infusion of the leaves containing an equivalent amount of arbutin to healthy volunteers had strong antibacterial activity, as measured in urine samples after adjustment of the urine pH to 8.0 (*25*).

Contraindications

During pregnancy (*33*) or lactation, or in children under the age of 12 years (*13*). Folium Uvae Ursi is also contraindicated in patients with kidney disorders (*12*).

Warnings

Folium Uvae Ursi should not be used for prolonged periods. Patients with persistent symptoms of a urinary tract infection should consult a physician. Use of Folium Uvae Ursi may cause a greenish-brown coloration of the urine that darkens on exposure to air due to the oxidation of hydroquinone.

Precautions

Drug interactions

Folium Uvae Ursi should not be administered with foods or medicines that acidify the urine.

Carcinogenesis, mutagenesis, impairment of fertility

Folium Uvae Ursi was not mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strains TA98 or TA100 (*34*, *35*). Hydroquinone was also not mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strains TA98, TA100, TA1535 or TA1537, with or without metabolic activation (*36*).

Although extracts of the leaves do not appear to be carcinogenic, there is some evidence that hydroquinone is carcinogenic. Treatment of F344/N rats with hydroquinone resulted in a marked increase in tubular cell adenomas of the kidney in males, and an increase in mononuclear cell leukaemia in females. There was also some evidence of carcinogenic activity of hydroquinone in female $B6C3F_1$ mice, as shown by an increase in hepatocellular neoplasms, mainly adenomas. There was no evidence, however, of carcinogenic activity of an aqueous extract of the leaves in male $B6C3F_1$ mice (treated by gavage with 50–100 mg extract/kg body weight) (*36*). The sources of human exposure to hydroquinone (including environmental sources) have been reviewed, as have data on its kinetics and metabolism, and its effects in animals and humans (*32*).

Arbutin was administered subcutaneously at 25, 100 or 400 mg/kg body weight daily to male rats before mating, and to female rats during pregnancy and lactation. No effect on reproduction of male and female rats, or the development of the offspring was observed at doses of up to 100 mg/kg body weight. Fetal toxicity was observed at doses of 400 mg/kg body weight (*37*).

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions.

Adverse reactions

Internal use of Folium Uvae Ursi may cause nausea and vomiting due to stomach irritation from the high tannin content (*13*, *38*). The hydroquinone concentration in topical preparations is limited to 2% in Nigeria, the United

Kingdom and the United States of America, following reports that preparations containing more than 2% hydroquinone caused exogenous ochronosis in black women in South Africa (*39*). Topical application of preparations containing less than 3% hydroquinone in different bases caused negligible effects in male volunteers from different racial groups. However, there are case reports suggesting that skin-lightening creams containing 2% hydroquinone have produced leukoderma as well as ochronosis. Hydroquinone (at a concentration of 1% in aqueous solution or 5% in a cream) has caused erythema and allergic contact dermatitis (*32*).

Dosage forms

Crude drug for infusions or cold macerates, extracts and solid forms for oral administration (*13*). Store in a well-closed container, protected from light (*3*).

Posology

(Unless otherwise indicated)

Daily dose: 3 g crude drug in 150 ml water as an infusion or cold macerate, up to three or four times daily; 400–850 mg hydroquinone derivatives. Other preparations accordingly calculated as arbutin (*12*, *13*).

Patients should avoid highly acidic foods, such as acidic fruits or fruit juice, during treatment (*25*, *40*), and be advised to drink plenty of fluids.

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World Health Organization

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Introduction

Increasing role of the WHO monographs on selected medicinal plants

Since 1999, WHO has published two volumes of the *WHO monographs on selected medicinal plants*. Volume 1 includes 28 monographs and volume 2 contains an additional 30 monographs. Both of these volumes are now available on the WHO web site http://www.who.int/medicines/organization/trm/orgtrmstrat.htm).

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role. For example, in the recent WHO global survey on national policy and regulation of herbal medicines, of the 34 countries reporting that they do not have their own national monographs and use other monographs, 13 use the WHO monographs as an authoritative reference. Moreover, the format of the WHO monographs continues to be commonly used for developing national monographs. In the same survey, of the 46 countries that have already developed national monographs on herbal medicines, several countries, such as Armenia, Bhutan, Brazil, Malaysia, and Myanmar, reported having used the WHO format as a basis.

In May 2002, WHO launched its Traditional Medicine Strategy covering the period 2002–2005. In 2003, the World Health Assembly adopted resolution WHA56.31 on traditional medicine, which requests WHO to seek, together with WHO collaborating centres, evidence-based information on the quality, safety and cost-effectiveness of traditional therapies. The objective is to provide guidance to Member States on the definition of products to be included in national directives and proposals on traditional-medicine policy implemented in national health systems. The continued development of the *WHO monographs on selected medicinal plants* is one of the important activities being undertaken to meet the demands from Member States and in the implementation of the WHO Traditional Medicine Strategy.

Preparation of monographs for volume 3

During the preparation of volume 3, more than 170 experts were involved, in addition to members of WHO's Expert Advisory Panel on Traditional

Medicine, a significant expansion in comparison to the numbers involved in the first two volumes. National drug regulatory authorities in 65 countries participated in the process, again a greater number than for the previous volumes. This global network of active players facilitated wider access to the available scientific references and information, in terms of both quality and quantity. This considerable level of support contributed greatly to the efficiency of the preparation process.

The Third WHO Consultation on Selected Medicinal Plants was held in Ottawa, Canada, in July 2001 to review and finalize the draft monographs. Thirty-two experts and drug regulatory authorities from WHO Member States participated (Annex 1). Following extensive discussion, 31 of the 33 draft monographs were adopted for inclusion.

At the subsequent tenth International Conference of Drug Regulatory Authorities held in China, Hong Kong Special Administrative Region in June 2002, the 31 draft monographs adopted for volume 3 of the *WHO monographs on selected medicinal plants* were presented. In its recommendations, the Conference requested WHO to publish them as soon as possible.

Selection of medicinal plants

The selection of medicinal plants for inclusion in the WHO monographs is based on worldwide use. The medicinal plants selected must meet two major criteria: (1) they must be in common use in at least two WHO Regions; and (2) there must be sufficient scientific data available to satisfy the requirements of the various sections in the monograph format.

The Third WHO Consultation on Selected Medicinal Plants discussed the selection criteria and made recommendations that will be applied starting with the preparation of volume 4 of the WHO monographs.

Changes in format in volume 3

Following intensive discussion at the Ottawa Consultation the title and context of the three categories included in the section Medicinal uses has been changed. The changes are described in the in the General technical notices.

It was also decided at the Ottawa Consultation that the section on Adverse reactions should be moved to follow immediately after the section on Pharmacology, to provide a more logical progression for the subsequent sections on Contraindications, Warnings and Precautions.

A description of selected sections of the monographs is given in the General technical notices, which reflect the above-mentioned format changes. For easy reference, two cumulative indexes are provided as an-

nexes. Annex 2 lists the monographs in alphabetical order of the plant name, while Annex 3 is according to the plant materials of interest.

Under the section "Geographical distribution", an attempt has been made to describe the geographical distribution of the plant, i.e. its natural distribution, where it is cultivated, and conditions of cultivation, harvesting and storage. This has been a challenge, owing to the lack of data based on established national good agricultural practices and/or good collection practices for medicinal plants. In 2003, WHO published the *WHO guidelines on good agricultural and collection practices* (*GACP*) *for medicinal plants*, which provide general technical guidance on obtaining medicinal plant materials of good quality for the sustainable production of herbal medicines in the overall context of quality assurance and control of herbal medicines. It is hoped that these guidelines will facilitate the development of GACP monographs on specific medicinal plants at national level, which in turn should bridge the current information gap in this area.

Purpose and content of monographs

The purpose of the monographs was clearly explained in the introduction to volume 1, and it is unnecessary to repeat it here. But I would like to emphasize again that the word "monograph" is used as a technical term only. It does not have the same meaning as "monograph" in any type of pharmacopoeia. In addition, I must reaffirm that this publication is not intended to replace any official compendia such as pharmacopoeias, formularies or legislative documents.

It should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

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General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO's Member States; to provide models to assist WHO's Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO's Member States.

The format used for volume 3 essentially follows that of volume 2. However, to keep relevant sections together, *Adverse reactions* appears immediately after the section on *Pharmacology*. The titles of three categories under the *Medicinal uses* have been changed to the following:

- *Uses supported by clinical data*
- *Uses described in pharmacopoeias and well established documents*
- *Uses described in traditional medicine*

The *Definition* provides the Latin binomial name, the most important criterion in quality assurance. Latin binomial synonyms and vernacular names, listed in *Synonyms* and *Selected vernacular names* respectively, are names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Code of Botanical Nomenclature. The vernacular names comprise an alphabetical list of selected names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. They refer to the medicinal plant itself not the medicinal plant part, which is identical to the monograph name. The lists are not complete, but reflect the names of the concerned medicinal plant appearing in the official monographs and reference books consulted and those in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, Chicago, IL, USA). While every effort has been made to delete names referring to the

medicinal plant part, the relevant section of each monograph may still include these.

Geographical distribution is not normally found in official compendia, but is included here to provide additional quality assurance information. The detailed botanical description under *Description* is intended for quality assurance at the stages of production and collection; the description of the crude drug material under *Plant material of interest* is for the same purpose at the manufacturing and commerce stages.

General identity tests, *Purity tests* and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with national requirements by the appropriate authorities of Member States.

Each medicinal plant and the specific plant part used as crude drug material contain active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the *Major chemical constituents*.

Descriptions included in *Medicinal uses* should not be taken as implying WHO's official endorsement or approval for such uses. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange.

The first category, *Uses supported by clinical data*, includes medical indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. Clinical trials may be controlled, randomized, double-blind studies, open trials, cohort studies or well documented observations on therapeutic applications.

The second category, *Uses described in pharmacopoeias and well established documents*, includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or governmental monographs. Uses having a pharmacologically plausible basis are also included, as well as information resulting from clinical studies that clearly need to be repeated because of conflicting results.

The third category, *Uses described in traditional medicine*, refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. Their appropriateness could not be assessed, because sufficient data to support the claims could not be found in the literature. Traditional uses that address severe pathologies, such as cancer, AIDS, hepatitis, etc., as they relate to these modern biomedical terms, should only be included under the third heading if pharmacological data

or robust ethnopharmacological/ethnobotanical reports are available to support the claims.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Abbreviated details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included, to avoid confusion.

The details included in the *References* have been checked against the original sources wherever possible. For references in languages other than English, except for those in Chinese and Japanese, the title is given in the original language, except in cases where an English summary is available.

Fructus Ammi Majoris

Definition
Fructus Ammi Majoris consists of the dried ripe fruits of *Ammi majus* L. (Apiaceae) (*1, 2*).

Synonyms
Apium ammi Crantz, *Selinum ammoides* E.H.L. Krause (*3*). Apiaceae are also known as Umbelliferae.

Selected vernacular names
Aatrilal, ammi commun, bishop's weed, bullwort, crow's foot, cumin royal, devil's carrot, gazar el-shitan, greater ammi, habab, herb william, hirz al-shayateen, khella shaitani, khellah shitany, mayweed, nounkha, qciba, rejl el-ghorab, rijl al-tair, zfenderi el maiz (*1, 2, 4–6*).

Geographical distribution
Indigenous to Egypt, and widely distributed in Europe, the Mediterranean region and western Asia. Cultivated in India (*2*).

Description
An annual, 0.9–1.5 m high with striated subglaucous stems. Leaves acutely serrulate, alternate, bipinnate, lobes oblong. Inflorescence a compound umbel with slender primary rays up to 5 cm long, scattered secondary rays 2–5 cm long, minute reticulate points; involucre of bracts 1.5–2.5 cm long; flowers bisexual, polygamous, bracteate; calyx teeth obsolete or small; petals obovate with an inflexed point, exterior petals frequently longer; stamens epigynous; ovary inferior, two-locular, stigma capitate. Fruit laterally compressed, oblong, mericarps of the cremocarp separated by a carpophore. Seed small, pendulous, albuminous (*2*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp nearly cylindrical, usually separated into its two mericarps, rarely entire, with a part of the pedicel attached. Mericarp small, slightly concave on the commissural side, slightly tapering towards the apex; 2.0–2.5 mm long, 0.75 mm wide, reddish-brownish to greenish-brown, crowned with a nectary, disc-like stylopod. Externally glabrous, rough, marked with five broad, distinct, yellowish-brown primary ridges, alternating with four equally prominent, dark brown secondary ridges. Internally comprises a pericarp with six vittae, four in the dorsal and two in the commissural side, and a large orthospermous endosperm in which is embedded a small apical embryo. Carpophore forked, each branch entering at the apex of the mericarp and uniting with the raphe (*1, 2*).

Organoleptic properties

Odour: slightly aromatic, terebinthinate; taste: aromatic, strongly pungent, slightly bitter (*1*).

Microscopic characteristics

Epidermis of the pericarp consists of polygonal cells, with straight anticlinal walls and short papillae, containing cluster or prismatic crystals of calcium oxalate, and covered with a strongly striated cuticle; stomata, occasionally of the anisocytic type, but with no trichomes. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, four in the dorsal and two in the commissural side, which appear elliptical in transverse section, each surrounded by large, radiating cells; traversed in the primary ridges by vascular bundles, which appear oval, ovoid or rounded in transverse section, not accompanied by vittae, each bundle with a xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres and reticulate, lignified cells. Innermost layer consists of large, polygonal, brown-walled cells, with thick, non-porous inner walls. Endocarp composed of narrow, tangentially elongated cells, many in regular arrangements in variously oriented groups (e.g. parquet arrangement), adhering to the brown seed coat, which is formed of similar but wider and shorter cells. Endosperm consists of polygonal, thick-walled, cellulosic parenchyma, containing fixed oil and several aleurone grains, 4–12 µm in diameter, each with one or two rounded globoid and one or two microrosette crystals of calcium oxalate, 2–5 µm in diameter. Carpophore, each branch traversed by a vascular bundle of fibres and spiral vessels (*1, 2, 7*).

Powdered plant material

Yellowish-brown and characterized by fragments of epicarp with polygonal, subrectangular or elongated, short, papillose cells, containing cluster or prismatic crystals of calcium oxalate, and covered with thick, distinctly striated cuticle. Also present are fragments of mesocarp with brownish pieces of vittae, reticulate cells, vessels and fibres; fragments of endocarpal cells with a distinct parquet arrangement, usually adhering to brown cells of the testa; numerous fragments of the endosperm containing colourless, polygonal cells, numerous oil globules and several aleurone grains, 4–12 µm in diameter, each enclosing microrosette crystals of calcium oxalate, 2–5 µm in diameter. Trichomes and starch grains absent (*1, 2*).

General identity tests

Macroscopic and microscopic examinations, microchemical tests (*1, 2*), and thin-layer chromatography for the presence of xanthotoxin and bergapten (*8*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

Total ash

Not more than 7% (*1, 2*).

Acid-insoluble ash

Not more than 0.04% (*2*).

Water-soluble extractive

Not less than 17% (*2*).

Alcohol-soluble extractive

Not less than 16% (*2*).

Loss on drying

Not more than 12% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

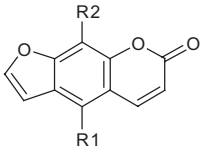
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.5% xanthotoxin, 0.3% imperatorin and 0.01% bergapten, determined by spectrophotometry (*1*). A high-performance liquid chromatography method is also available for quantitative analysis (*12*).

Major chemical constituents
The major constituents are furanocoumarins, the principal compounds being xanthotoxin (methoxsalen, 8-methoxypsoralen (8-MOP) ammoidin; up to 1.15%), imperatorin (ammidin; up to 0.75%) and bergapten (heraclin, majudin, 5-methoxypsoralen (5-MOP), up to 1.88%). Other coumarins of significance are marmesin (up to 0.25%), isoimperatorin (0.01%), heraclenin (0.07%) and isopimpinellin (0.01%). Other constituents of interest are acetylated flavonoids (*13–17*). The structures of xanthotoxin, imperatorin and bergapten are presented below.



furanocoumarins	R1	R2
bergapten	OCH_3	H
imperatorin	H	$O\text{-}CH_2\text{-}CH{=}C(CH_3)_2$
xanthotoxin	H	OCH_3

Medicinal uses
Uses supported by clinical data
Treatment of skin disorders such as psoriasis and vitiligo (acquired leukoderma) (*1, 5, 18–26*).

Uses described in pharmacopoeias and well established documents
Treatment of vitiligo (*1*).

Uses described in traditional medicine

As an emmenagogue to regulate menstruation, as a diuretic, and for treatment of leprosy, kidney stones and urinary tract infections (*6*).

Pharmacology

Experimental pharmacology

Antimicrobial and antischistosomal activities

A 50% dilution of an acetone or 95% ethanol extract of Fructus Ammi Majoris inhibited the growth of the fungus *Neurospora crassa* in vitro (*27*). Intragastric administration of 400.0 mg/kg body weight (bw) of a hot aqueous extract or 15.0 mg/kg bw of a petroleum ether extract of the fruits per day for 6 days reduced the *Schistosoma mansoni* worm burden in mice by 49.3–72.3% (*15*).

Miscellaneous effects

Intragastric administration of 500.0 mg/kg bw of the powdered fruits per day to rats for 4 weeks did not reduce the incidence of glycolic acid-induced kidney stones (*28*).

Photosensitizing effects

Xanthotoxin is available in synthetic form and is a known photosensitizing agent and antipsoriatic. The augmented sunburn reaction involves excitation of the drug molecule by radiation in the long-wave ultraviolet (UV) A range. The transfer of energy to the drug molecule produces a triplet electronic state. The excited molecule then binds covalently with cutaneous DNA, forming a cyclobutane ring with the DNA pyrimidine bases, within the epidermal cells of the skin. In this manner, xanthotoxin inhibits nuclear division and cell proliferation (*21, 22, 29*).

Toxicology

Intoxication due to the simultaneous ingestion of ergot alkaloids from *Claviceps purpurea* sclerotia and furanocoumarins from *Ammi majus* seeds was reported in pigs after ingestion of contaminated feed. Nervous system intoxication was first observed 5–7 days after the initiation of feeding of the suspect rations. This was followed by cutaneous irritation, including snout ulcers, eyelid oedema and conjunctivitis. Ten days after the feeding, eight abortions were observed and, in nursing sows, udder oedema and teat cracking were observed. Examination of the adulterated feed indicated that it contained 2.2% *A. majus* seeds and 0.14% *C. purpurea* sclerotia. Quantitative analysis showed the presence of 3.2 g of xanthotoxin and 0.65 g of imperatorin per 100 g of *A. majus* seeds, and 0.73 g of ergot alkaloids per 100 g of *C. purpurea* sclerotia (*30*).

The median lethal doses (LD_{50}) of xanthotoxin, imperatorin and bergapten injected into the ventral lymph sac of toads were 13.8 mg/100 g bw, 14.0 mg/100 g bw and 32.0 mg/100 g bw, respectively. In rats, the intramuscular LD_{50} values were 16.0 mg/kg bw, 33.5 mg/kg bw and 94.5 mg/kg bw, respectively (*31*).

After 4–8 days of administration of 2 g of *A. majus* seeds per day to 3- to 5-week-old goslings in the diet, the animals became photosensitive. Photosensitivity appeared after 4–5 hours of exposure to sunlight and was characterized by erythema, haematomas and blisters on the upper side of the beak (*32*). The photoirritant effects of five constituents of *A. majus* seeds, xanthotoxin, imperatorin, isopimpinellin, bergapten and isoimperatorin, were evaluated in the mouse-ear assay. Isoimperatorin was the most irritant compound (median irritant dose (ID_{50}) 0.0072 mg after 5 days of treatment), while imperatorin was the least irritant (ID_{50} 0.3823 mg after 6 days of treatment). The three other compounds showed minimal photoirritant activity (*33*).

Chronic toxicity in the form of decreases in the red blood cell count and haemoglobin A concentration was observed in mice after administration of 100.0 mg/kg bw of a 95% ethanol extract of the fruits in drinking-water (*34*). Administration of 6.2–18.9 g/kg bw of the fruits per day in the diet to cattle and sheep for 49 days caused photosensitization in both species (*35*). Ingestion of *A. majus* seeds together with exposure to sunlight caused mydriasis in geese and ducks (*36*). Chronic 7-week exposure of ducks and geese to the fruits (dose not specified) caused severe deformities of the beak and footwebs, mydriasis and ventral displacement of the pupils (*37, 38*). Ophthalmological examination of the animals revealed dense pigmentation in the fundus (pigmentary retinopathy) and hyperplasia of the retinal pigment epithelium (*36, 39*). The iris showed varying degrees of atrophy of the sphincter pupillae (*36*).

Intragastric administration of a single dose of 8.0 g/kg bw of the fruits to sheep produced cloudy cornea, conjunctivokeratitis, photophobia and oedema of the muzzle, ears and vulva (*40*). Intragastric administration of 2.0 g/kg or 4.0 g/kg bw per day produced similar symptoms after 72–96 hours (*40*).

Clinical pharmacology

Numerous clinical trials have assessed the efficacy of Fructus Ammi Majoris and xanthotoxin for the treatment of vitiligo, psoriasis and hypopigmentation tinea versicolor (*18–20, 41–44*).

The powdered fruits (dose not specified) were administered orally to leukodermic patients, who then exposed the affected patches to direct sunlight for 1 hour. The patients subsequently developed symptoms of

itching, redness, oedema, vesiculation and oozing in the leukodermic patches. A few days later the affected skin gradually started to display deep brown pigmentation. Repigmentation usually developed within 1 week, in a punctate or perifollicular fashion, spreading inwards from the margin or diffuse (*5*). In a small clinical trial without controls, two groups of eight patients with leukoderma were treated orally with 0.05 g of xanthotoxin three times per day or in the form of a liniment, 1 g/100 ml, applied to the skin. The patients then exposed the leukodermic areas to the sun for 0.5 hour or to UV light for 2 minutes, gradually increasing to 10 minutes, per day. After treatment, the leukodermic skin areas were inflamed and vesiculated, and were treated as second-degree burns. When healing occurred these areas began to show normal pigmentation (*19*).

Since 1966, over 100 clinical studies have investigated the safety and efficacy of xanthotoxin for the treatment of a wide range of ailments including vitiligo and psoriasis, in a variety of dosage forms and routes of administration. The drug is now accepted as standard medical therapy for the symptomatic control of severe, recalcitrant, disabling psoriasis that does not respond to other therapy, diagnosis being supported by biopsy. Xanthotoxin should be administered only in conjunction with a schedule of controlled doses of long-wave UV radiation. It is also used with long-wave UV radiation for repigmentation of idiopathic vitiligo (*29*). While a review of all the clinical studies is beyond the scope of this monograph, some of the more recent data are presented below.

A comparative trial involving 34 patients with plaque psoriasis assessed the efficacy of xanthotoxin administered by two different routes in combination with exposure to UV-A light. Each group of 17 patients was treated with the drug delivered either orally or in bath-water. Both treatments were effective; however, bath treatments were as effective or more effective than oral treatment and required less than half the dose of UV-A radiation required in the oral treatment group. Bath treatments also caused fewer side-effects (*26*).

A randomized, double-blind, right-left comparison trial investigated the efficacy of a combination of xanthotoxin plus UV-A radiation with topical calcipotriol in the treatment of vitiligo. Nineteen patients with bilateral symmetrical lesions were treated with an oral dose of 0.6 mg/kg bw of xanthotoxin 2 hours before exposure to sunlight three times per week. The patients were instructed to apply calcipotriol ointment at 50 µg/g on one side of the body and placebo ointment on the other. At the end of 6 months, 70% of patients showed significant improvement on the calcipotriol-treated side as compared with 35% on the placebo-treated

side ($P < 0.05$). It was concluded that the combination of xanthotoxin and calcipotriol is highly effective for the photochemotherapy of vitiligo (*25*).

A randomized comparison trial assessed the efficacy of xanthotoxin plus exposure to either UV-A or UV-B radiation for the treatment of plaque psoriasis in 100 patients. Both treatments were effective in reducing the number of plaques; no significant difference between the treatments was observed (*24*).

The efficacy of two UV-A radiation dosage regimens for treatment with oral administration of 0.6 mg/kg bw of xanthotoxin plus UV-A photochemotherapy for moderate–severe chronic plaque psoriasis was assessed using a half-body comparison. The high- and low-dose UV-A treatments were administered twice per week and symmetrical plaques were scored to determine the rate of resolution for each treatment. Patients were reviewed monthly for 1 year and 33 patients completed the study. Both regimens were effective and well tolerated; 42% of patients were clear 1 year after treatment and, for those whose psoriasis had recurred, there was no significant difference between the regimens in the number of days of remission (*23*).

In a clinical trial without controls, the efficacy of xanthotoxin in 10-mg capsules was assessed for the treatment of psoriasis, vitiligo and tinea versicolor (*43*). Fifty-three patients were treated orally with 0.25 mg/kg bw of xanthotoxin and then exposed to UV-A light for varying periods of time. In 87% of psoriasis patients, remission occurred after 30 treatments with xanthotoxin and UV-A, 85% of patients with vitiligo had acceptable repigmentation after 70 treatments, and 100% of patients with hypopigmentation tinea versicolor showed complete repigmentation after 12 treatments (*43*).

Exposure to Fructus Ammi Majoris or xanthotoxin in combination with exposure to UV-A light elicits a cutaneous inflammation, including erythema, oedema and bullae. The inflammatory processes culminate after 72 hours and hyperpigmentation appears after 1–2 weeks, lasting for several months. The mechanism of repigmentation is still a matter of debate. Affected cells may include keratinocytes, Langerhans cells and melanocytes in the epidermis as well as mononuclear and endothelial cells in the upper dermis. Epidermal changes include dyskeratosis, mild spongiosis and intracellular oedema at 24 hours, increasing at 72 hours. After 72 hours there is an increased mitotic activity in melanocytes and an increased number of functional melanocytes, with rises in the production of melanosomes and tyrosinase activity (*45*). Hyperpigmentation is due to the increased number of melanin granules in the epidermis, both in the Malpighian stratum and in the hyperkeratotic stratum corneum (*46, 47*).

Adverse reactions

One case of phototoxic dermatitis was reported in a patient with vitiligo after ingestion of Fructus Ammi Majoris (*48*). One case of allergic rhinitis and contact urticaria due to exposure to the fruits was reported (*49*). Phototoxic reactions were reported in subjects who handled the fruits and were subsequently exposed to sunlight. Erythema developed within 48–72 hours and persisted for several days. Skin that had been protected from sunlight for 30 days after exposure still had many erythematous areas and became irritated again when re-exposed to the sun. Small areas of darker pigmentation developed in the skin of some subjects (*35*). Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache, allergic symptoms and sleeplessness (*50*).

Photochemotherapy combining administration or application of xanthotoxin with UV-light treatment can be repeated many times (four times a week), and after about 14 days of therapy, a clear dilution of the epidermis results, cornification normalizes and the inflammation fades away. However, overdosage may result in severe erythema and blistering. This can partly be prevented through the application of β-carotene (*51*).

A 5-year prospective study of ophthalmological findings in 1299 patients treated with oral xanthotoxin plus UV photochemotherapy for psoriasis failed to demonstrate a significant dose-dependent increase in the risk of developing cataracts (*52*).

Other adverse reactions reported after treatment with xanthotoxin include itching, nausea, oedema, hypotension, nervousness, vertigo, depression, painful blistering, burning and peeling of the skin, pruritus, freckling, hypopigmentation, rash, cheilitis and erythema (*29*).

Contraindications

Fructus Ammi Majoris is contraindicated in diseases associated with photosensitivity, cataract, invasive squamous-cell cancer, known sensitivity to xanthotoxin (psoralens), and in children under the age of 12 years (*29*). The fruits are also contraindicated in pregnancy, nursing, tuberculosis, liver and kidney diseases, human immunodeficiency virus (HIV) infections and other autoimmune diseases (*22*).

Warnings

Care should be taken where there is a familial history of sunlight allergy or chronic infections; lotions should be applied only under direct supervision of a physician and should not be dispensed to the patient; for use only if response to other forms of therapy is inadequate. Serious burns

may result from exposure to UV-A light or sunlight, even through glass, if the correct dose and exposure schedule is not maintained.

If burning, blistering or intractable pruritus occurs, discontinue therapy until side-effects subside. Do not sunbathe for at least 24 hours prior to therapy and 48 hours after. Avoid direct and indirect sunlight for up to 8 hours after oral and 12–48 hours after topical treatment. If sunlight cannot be avoided, protective clothing and/or sunscreen must be worn. Following oral therapy, sunglasses must be worn for 24 hours. Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard and carrots (*29*).

Precautions

Drug interactions

The toxicity of Fructus Ammi Majoris may be increased when the fruits are administered with other photosensitizing agents such as coal tar, dithranol, griseofulvin, nalidixic acid, phenothiazines, sulfanilamides, tetracyclines and thiazides (*22, 29*).

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Ammi Majoris, 10.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102. Furthermore, an infusion of the fruits (concentration not specified) had antimutagenic effects against ethyl methanesulfonate- or 2-amino-anthracene-induced mutagenicity in *S. typhimurium* strains TA98 and TA100 (*53*).

A study of 4799 Swedish patients who received xanthotoxin/UV-A photochemotherapy in the period 1974–1985 showed a dose-dependent increase in the risk of squamous-cell cancer of the skin. Male patients who had received more than 200 treatments had over 30 times the incidence of squamous-cell cancer compared with the general population. Increases in the incidence of respiratory cancer, pancreatic cancer and colon cancer were also found (*54*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms

Powdered dried fruits for oral use (*1*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: Fructus Ammi Majoris 0.02–0.04 g orally in divided doses (dosage schedule not specified) (*1*); xanthotoxin 0.25–0.7 mg/kg bw (*18, 20, 43*). Clinical treatment requires management by a health-care provider.

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Fructus Ammi Visnagae

Definition

Fructus Ammi Visnagae consists of the dried ripe fruits of *Ammi visnaga* (L.) Lam. (Apiaceae) (*1–3*).

Synonyms

Daucus visnaga L., *Selinum visnaga* E.H.L. Krause, *Sium visnaga* Stokes, *Visnaga daucoides* Gaertn. (*2, 4*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Ammi, besnika, bisagna, bishop's weed, herbe aux cure-dents, herbe aux gencives, kella, kella balady, khelâl dandâne, khella, nunha, owoc keli, Spanish carrot, viznaga, Zahnstocherkraut (*2, 5–8*).

Geographical distribution

Indigenous to the Mediterranean region. Cultivated in North America and in Argentina, Chile, Egypt, India, Islamic Republic of Iran, Mexico, Tunisia and Russian Federation (*2, 5–7*).

Description

An annual or biennial herb, up to 1.0 m high. Leaves dentate, in strips. Stems erect, highly branched. Inflorescence umbellate; rays, highly swollen at the base, become woody and are used as toothpicks. Fruits as described below (*2, 6*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp usually separated into its mericarps; rarely, occurs entire with a part of the pedicel attached. Mericarp small, ovoid, about 2 mm long, 1 m wide, brownish to greenish-brown, with a violet tinge. Externally glabrous, marked with five distinct, pale brownish, broad primary ridges, four inconspicuous, dark secondary ridges, and a disc-like stylopod at the apex. Internally comprises a pericarp with six vittae, four in the dorsal and two in the

commissural side, a large oily orthospermous endosperm and a small apical embryo. Carpophore single, passing into the raphe of each mericarp (*1, 2*).

Organoleptic properties

Odour: slightly aromatic; taste: aromatic, bitter, slightly pungent (*1, 2*).

Microscopic characteristics

Epidermis of the pericarp consists of polygonal cells, elongated on the ridges, with occasional crystals of calcium oxalate and finely striated cuticle, but no hairs. Mesocarp consists of parenchyma, traversed longitudinally by large, schizogenous vittae, each surrounded by large, slightly-radiating cells, and in the ridges by vascular bundles, each forming a crescent around a comparatively large lacuna and accompanied by fibres and reticulate, lignified cells. Innermost layer consists of large, polygonal, brown-walled cells, with thick, porous inner walls. Endocarp composed of narrow tangentially elongated cells, some of which are in regular arrangements in variously oriented groups, adhering to the brown seed coat, which is formed of similar but wider, shorter cells. Endosperm consists of polygonal, thick-walled, cellulosic parenchyma containing fixed oil and numerous small, oval aleurone grains, each enclosing a minute, rounded globoid and a microrosette crystal of calcium oxalate. Carpophore, passing at the apex into the raphe of each mericarp, traversed by a vascular bundle of fibres and spiral vessels (*1, 2*).

Powdered plant material

Brown and characterized by fragments of pericarp with some brownish pieces of vittae, reticulate cells, vessels and fibres. Also present are fragments with inner porous mesocarp cells crossed by and intimately mixed with variously oriented groups of endocarpal cells; and numerous fragments of endosperm. Other fragments show cells of the brown seed coat and aleurone grains 4–10 µm in diameter, containing microrosette crystals of calcium oxalate 2–5 µm in diameter. Hairs and starch grains absent (*1, 2*).

General identity tests

Macroscopic and microscopic examinations, microchemical tests (*1–3*), and thin-layer chromatography for the presence of khellin and visnagin (*3, 6, 9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter
Not more than 2% (*3*).

Total ash
Not more than 8% (*2*).

Acid-insoluble ash
Not more than 3.5% (*1*).

Loss on drying
Not more than 10% (*3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

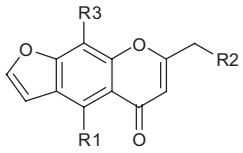
Chemical assays

Contains not less than 1% γ-pyrones (furanochromone derivatives) calculated as khellin, determined by spectrophotometry (*1–3*). A number of high-performance liquid chromatography methods are also available for quantitative analysis (*13–17*).

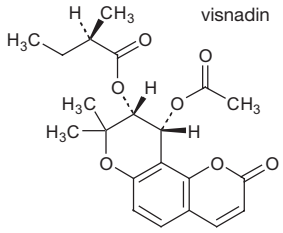
Major chemical constituents

The major constituents are γ-pyrones (furanochromone derivatives; up to 4%), the principal compounds being khellin (0.3–1.2%) and visnagin (0.05–0.30%). Other γ-pyrones of significance are khellinol, ammiol, khellol and its glucoside khellinin (0.3–1.0%). A second group of major constituents are the coumarins (0.2–0.5%), the main one being the

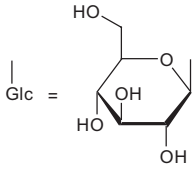
pyranocoumarin visnadin (0.3%). Essential oil contains camphor, α-terpineol and linalool, among others, and also fixed oil (up to 18%) (*6, 8, 13–15, 18, 19*). Representative structures are presented below.



	R1	R2	R3
ammiol	OCH_3	OH	OCH_3
khellin	OCH_3	H	OCH_3
khellinin	OCH_3	O-Glc	H
khellinol	OH	H	OCH_3
khellol	OCH_3	OH	H
visnagin	OCH_3	H	H



visnadin



β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As an antispasmodic, muscle relaxant and vasodilator (*1*).

Uses described in traditional medicine

Treatment of mild anginal symptoms. Supportive treatment of mild obstruction of the respiratory tract in asthma, bronchial asthma or spastic bronchitis, and postoperative treatment of conditions associated with the presence of urinary calculi. Treatment of gastrointestinal cramps and painful menstruation (*6*). Internally as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of vertigo, diabetes and kidney stones (*8*).

Pharmacology

Experimental pharmacology

Antimicrobial activities

A 50% acetone, 50% aqueous or 95% ethanol extract of Fructus Ammi Visnagae inhibited the growth of the fungus *Neurospora crassa* in vitro

(*20*). A 95% ethanol extract of the fruits inhibited the growth of *Mycobacterium tuberculosis* H37RVTMC 102 at a dilution of 1:40 in vitro (*21*). An aqueous extract of the fruits, 2–10 mg/ml inhibited growth and aflatoxin production by *Aspergillus flavus*; the effects were dose-dependent (*22*).

Antispasmodic effects

A methanol extract of the fruits, 1.0 mg/ml, inhibited potassium chloride-induced contractions in rabbit aorta in vitro (*23*). A chloroform extract of the fruits (concentration not specified) inhibited potassium chloride-induced contractions in guinea-pig aorta in vitro (*24*). Visnadin inhibited carbaminoylcholine- and atropine-induced contractions in isolated guinea-pig ileum at concentrations of 8.8 µmol/l and 0.02 µmol/l, respectively (*25*). Visnagin, 1.0 µmol/l, inhibited the contractile responses in rat aortic rings induced by potassium chloride, norepinephrine and phorbol 12-myristate 13-acetate, and spontaneous myogenic contractions of rat portal veins. Visnagin appears to inhibit only contractions mediated by calcium entry through pathways with low sensitivity to classical calcium channel blockers (*26, 27*).

Cardiovascular effects

Visnadin, 60.0 µg/ml or 120.0 µg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% and blood flow in a Laewan-Trendelenburg frog vascular preparation by 78% and 147%, respectively (*25*). Interarterial administration of 10.0 mg/kg body weight (bw) of visnadin to anaesthetized dogs increased blood flow by 30–100%, the effect lasting for 20 minutes after administration (*25*). Six compounds isolated from the fruits were tested for their ability to dilate coronary blood vessels in rabbits. Coronary vasospasm and myocardial ischaemia were induced by daily intramuscular injections of vasopressin tannate. All compounds were administered at 4.7 mg/kg bw per day by intramuscular injection for 7 days. Visnadin, dihydrosamidin, khellin and samidin effectively normalized the electrocardiogram, while visnagin and khellol glucoside were inactive (*28*). Positive inotropic effects were observed in dogs treated with intramuscular injections of samidin and khellol glucoside. No effects were observed for visnadin, dihydrosamidin, khellin and visnagin at varying doses (*28*).

Toxicology

In mice, the oral and subcutaneous median lethal doses (LD_{50}) of the fruits were 2.24 g/kg bw and > 370.0 mg/kg bw, respectively (*25*). In rats, the oral LD_{50} was > 4.0 g/kg bw, and in rabbits, the intravenous LD_{50} was

50.0 mg/kg bw. In dogs, the oral and intravenous LD_{50} values were 20.0 mg/kg bw and 200.0 mg/kg bw, respectively.

Subchronic oral administration of visnadin to mice, rats and rabbits at doses of up to 2.2 g/kg bw, up to 600.0 mg/kg bw and 6.0 mg/kg bw, respectively, produced no pronounced toxicity (*25*). In dogs, daily intramuscular injections of isolated chemical constituents of the fruits at ten times the therapeutic concentration for 90 days produced toxic effects characterized by increases in the serum glutamic-pyruvic and glutamic-oxaloacetic transaminases, increases in plasma urea, haematological changes and, in some cases, death. Of the six compounds tested, samidin was the most toxic, dihydrosamidin was the least toxic and khellin, visnagin, visnadin and khellol glucoside were of intermediate toxicity (*29*). The acute toxicities of khellin, visnagin, visnadin and samidin were assessed in mice and rats after intramuscular injection of doses of 0.316–3.16 mg/kg bw. The LD_{50} values were: khellin, 83.0 mg/kg bw in mice and 309.0 mg/kg bw in rats; visnagin, 123.0 mg/kg bw and 831.0 mg/kg bw; visnadin, 831.8 mg/kg bw and 1.213 g/kg bw; and samidin, 467.7 mg/kg bw and 1.469 g/kg bw (*30*).

Administration of *Ammi visnaga* seeds at 1.25–3% in the diet for 14 days had no toxic effects on turkeys or ducks. However, in chickens, the 3% dose produced mild signs of photosensitization within 6–8 days (*31*). Administration of 2.0 g/day for 4–8 days to goslings at age 3–5 weeks induced photosensitivity in the form of erythema, haematomas and blisters on the upper side of the beak (*32*).

The chemical constituents responsible for the induction of contact dermatitis in the mouse-ear assay were khellol, visnagin and khellinol, median irritant doses 0.125 µg/5 µl, 1.02 µg/5 µl and 0.772 µg/5 µl, respectively (*33*).

Clinical pharmacology

A placebo-controlled study assessed the effects of oral administration of 50 mg of khellin four times per day for 4 weeks on the plasma lipids of 20 non-obese, normolipaemic male subjects. Plasma lipids were measured every week during treatment and 1 week after cessation. Plasma total cholesterol and triglyceride concentrations remained unchanged, while high-density-lipoprotein cholesterol concentrations were significantly elevated, the effect lasting until 1 week after cessation of treatment (*34*).

Adverse reactions

Pseudoallergic reactions and reversible cholestatic jaundice have been reported (*35*). High oral doses of khellin (100.0 mg/day) reversibly elevated

the activities of liver transaminases and γ-glutamyltransferase (*35*). Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache and sleeplessness (*6*).

Contraindications

Fructus Ammi Visnagae is used in traditional systems of medicine as an emmenagogue (*8*), and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, the fruits should not be used during pregnancy.

Warnings

No information available.

Precautions

General

Exposure to sun or other sources of ultraviolet light should be avoided during treatment because khellin causes photosensitivity (*35*).

Drug interactions

No drug interactions have been reported. However, khellin is reported to inhibit microsomal cytochrome P450 subenzymes, and may therefore decrease the serum concentrations of drugs metabolized via this pathway, such as ciclosporin, warfarin, estrogens and protease inhibitors (*36*).

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Ammi Visnagae, 10.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102. Furthermore, an infusion of the fruits had antimutagenic effects against ethyl methanesulfonate- or 2-amino-anthracene-induced mutagenicity in *S. typhimurium* strains TA98 and TA100 (*37*). Khellin also inhibited the mutagenicity of promutagens such as benzopyrene, 2-aminofluorene and 2-aminoanthracene in *S. typhimurium* TA98. However, there was no effect on direct-acting mutagens, such as 2-nitrofluorene, 4-nitro-*o*-phenylenediamine, in *S. typhimurium* TA100 (*36*).

Pregnancy: teratogenic effects

Intragastric administration of up to 600.0 mg/kg bw of visnadin to rats on days 8–12 of pregnancy produced no toxic effects (*25*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers
Owing to the lack of safety data, Fructus Ammi Visnagae should be taken internally only under the supervision of a health-care provider.

Paediatric use
Owing to the lack of safety data, Fructus Ammi Visnagae should be taken internally only under the supervision of a health-care provider.

Other precautions
No information available on precautions concerning drug and laboratory test interactions.

Dosage forms
Dried fruits, infusions, extracts and other galenical preparations (*35*). Store fully dried fruits in well closed containers in a cool and dry place protected from light (*1*).

Posology
(Unless otherwise indicated)
Average daily dose: Fructus Ammi Visnaga 0.05–0.15 g (*1*).

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Fructus Anethi

Definition

Fructus Anethi consists of the dried ripe fruits of *Anethum graveolens* L. (Apiaceae) (*1*, *2*).

Synonyms

Pastinaca anethum Spreng., *Peucedanum graveolens* Benth. & Hook., *Selinum anethum* Roth (*1*, *3*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aneth, anethum, bo-baluntshep, dill, Dill-Fenchel, eneldo, faux anis aneth, fenouil bâtard, fenouil puant, garden dill, Gartendill, hinan, inondo, jirashi, kapor, kerwiya amya, koper, sadapa, sadhab el barr, satakuppa, satakuppi, sathukuppa, satpushpa, shabat, shabath, shatapuspi, shebet, shebid, sheved, shevid, shi ra ja, shibth, sibt, slulpha, soolpha, sova, sowa, s-sebt, suva, sulpha, sutopsha, thian ta takkataen, zira (*1*, *4–9*).

Geographical distribution

Indigenous to southern Europe. Cultivated widely throughout the world (*1*, *4*, *5*, *8*, *10*, *11*).

Description

An aromatic annual or biennial herb, 40–120 cm high, with an erect hollow green stem, branching above. Leaves glaucous, tripinnate, with linear leaflets. Inflorescence umbellate with 15–30 rays; bracts and bracteoles absent; flowers yellow. Fruits deep brown, flattened, oval, with protruding clear back ribs with sharp edges (*1*, *5*, *11–13*).

Plant material of interest: dried ripe fruits

General appearance

Mericarps separate, broadly oval, chocolate-brown, each dorsally compressed, 3–4 mm long, 2–3 mm wide and 1 mm thick, the ratio of length

to width being approximately 1.6:1.0; two ventral ridges prolonged into wide yellowish membranous wings; three dorsal ridges, brown, inconspicuous. Transversely cut surface of the fruit surface shows six vittae, four in the dorsal and two in the commissural side; five vascular bundles, three in the ridges and two in the wings, those in the wings being wider than those in the ridges (*1, 4, 5*).

Organoleptic properties

Odour: characteristic, aromatic; taste: characteristic, pleasant (*1, 4, 5*).

Microscopic characteristics

Mericarp has four vittae in the dorsal and two in the commissural side. Outer epidermis has a striated cuticle. Mesocarp contains lignified, reticulate parenchyma. Inner epidermis composed of tabular cells frequently with wavy walls, tabular cells all parallel (e.g. parquet arrangement). Thick-walled parenchyma of the endosperm contains fixed oil, aleurone grains and microrosette crystals of calcium oxalate (*1, 4, 14, 15*).

Powdered plant material

Greyish-brown powder characterized by fragments of pericarp with a few brownish pieces of vittae. Outer epidermis has striated cuticle. Mesocarp fragments show lignified reticulate parenchyma, inner epidermis, tabular cells frequently wavy walled, numerous fragments of endosperm; aleurone grains, fixed oil and microrosette crystals of calcium oxalate (*1*).

General identity tests

Macroscopic and microscopic examinations (*1, 2*), and thin-layer chromatography (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Chemical

Not less than 3.0% essential oil (*2*).

Foreign organic matter

Not more than 2.0% (*1*).

Total ash
Not more than 11.0% (*1*).

Acid-insoluble ash
Not more than 1.5% (*2*).

Water-soluble extractive
Not less than 15.0% (*2*).

Alcohol-soluble extractive
Not less than 4.0% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Other purity tests
Loss on drying test to be established in accordance with national requirements.

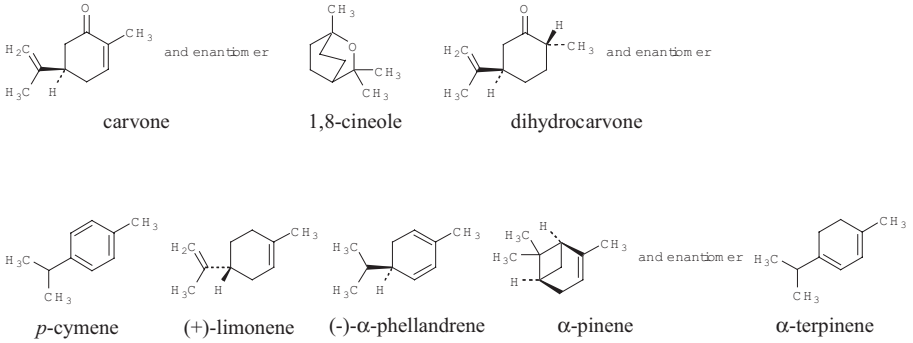
Chemical assays

Contains not less than 2.0% essential oil (*1*). Gas chromatography (*19*) and gas chromatography–mass spectrometry (*20*) methods for essential oil constituents are also available.

Major chemical constituents

Contains 2–5% essential oil, the major constituent of which is carvone (20–60%) (*11, 21, 22*). The carvone content in plants cultivated in India is reported to be 6% less than in those cultivated in Europe (*9*). Other characteristic terpenoid essential oil constituents include dihydrocarvone, 1,8-cineole, *p*-cymene, limonene, α-phellandrene, α-pinene and α-terpinene. The flavonoids present include kaempferol-glucuronide (*22, 23*).

Dillapiol is found in the essential oil obtained from plants cultivated in Egypt, India and Japan (*24*). Representative structures are presented below.



carvone 1,8-cineole dihydrocarvone

p-cymene (+)-limonene (-)-α-phellandrene α-pinene α-terpinene

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Treatment of dyspepsia (*25*), gastritis and flatulence (*1, 26*), and stomach ache (*27*).

Uses described in traditional medicine

As an aphrodisiac, analgesic, antipyretic, diuretic, emmenagogue, galactagogue, appetite stimulant and vaginal contraceptive. Treatment of diarrhoea, asthma, neuralgia, dysuria, dysmenorrhoea, gallbladder disease, insomnia, hiatus hernia and kidney stones (*9, 26–29*).

Pharmacology

Experimental pharmacology

Antispasmodic and carminative activities

A 50% ethanol extract of Fructus Anethi inhibited acetylcholine- and histamine-induced contractions of guinea-pig ileum in vitro (*30*). The essential oil, 50 mg/ml, reduced contractions of rabbit intestine (*31*). The essential oil (containing the monoterpenes and phenylpropanes: dillapiol, myristicin and isomyristicin) (concentration not specified) acted as a mild carminative and stomachic (*32*). The essential oil had carminative activity and reduced foaming in vitro, median effective concentration 2.0% (*33*).

Anti-inflammatory and analgesic activities

A single topical application of an ethanol extract of the fruits, at a dose corresponding to 1.0 mg/20 µl of a 10.0-mg dried methanol extract dissolved in 200.0 µl of ethanol, to the inner and outer surface of the ear of

mice inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13 acetate by 60% (*34*). Ethyl acetate and hexane extracts of the fruits (concentration not specified) were inactive in this assay. A 10% aqueous extract of the fruits and a 5% aqueous solution of the essential oil had analgesic effects in mice as assessed in the hot plate and acetic acid writhing tests. The action of the fruits at 1.0 g/kg body weight (bw) was comparable with that of acetylsalicyclic acid at 200.0 mg/kg bw (*35*).

Miscellaneous effects

Intravenous administration of 12.5 mg/kg bw of a 70% dried ethanol extract of the fruits, dissolved in normal saline, to dogs had a diuretic effect, with a 2.2-fold increase in urine output. Intravenous administration of 25.0 mg/kg bw of a 70% ethanol extract to dogs reduced blood pressure. Intravenous administration of 4.0 µl/kg bw of the essential oil induced diuresis in dogs lasting 80 minutes, with increased sodium and calcium ion excretion (*36*). Intravenous administration of 5.0–10.0 mg/kg bw of a 5% seed oil in saline to cats increased respiration volume and lowered blood pressure; intraperitoneal administration of 35.0 mg/kg bw of the seed oil to guinea-pigs induced anaphylactic shock (*11*). A single intragastric dose of 250.0 mg/kg bw of a 50% ethanol extract of the fruits to fasted rats reduced blood glucose levels by 30% compared with controls (*30*).

Toxicology

In a report by a national regulatory authority "generally regarded as safe status" was granted to Fructus Anethi as a flavouring agent in 1976 (*37*).

Clinical pharmacology

No information available.

Adverse reactions

Allergic reactions to Fructus Anethi including oral pruritus, tongue and throat swelling and urticaria, as well as vomiting and diarrhoea were reported in one patient with a history of allergic rhinitis (*38*).

Contraindications

Traditionally, extracts of fruits (seeds) have been used as a contraceptive and to induce labour (*4*). Furthermore, extracts of the fruits may have teratogenic effects (*39*). Therefore, the use of Fructus Anethi during pregnancy and nursing is not recommended.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A chloroform–methanol (2:1) extract of the fruits was not mutagenic in concentrations up to 100.0 mg/plate in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, with or without metabolic activation. A 95% ethanol extract was also without mutagenic activity in the same test system (*40*).

An essential oil prepared from the fruits was cytotoxic to human lymphocytes in vitro, and was active in the chromosome aberration and sister chromatid exchange tests in the same system. The oil was inactive in the *Drosophila melanogaster* somatic mutation and recombination test in vivo (*41*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic effects during pregnancy; or paediatric use.

Dosage forms

Dried fruits for teas, essential oil and other galenical preparations for internal applications. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: Fructus Anethi 3 g; essential oil 0.1–0.3 g; or equivalent for other preparations (*25*).

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Aetheroleum Anisi

Definition

Aetheroleum Anisi consists of the essential oil obtained by steam distillation from the dry ripe fruits of *Pimpinella anisum* L. (Apiaceae) (*1–5*).[1]

Synonyms

Anisum officinarum Moench, *A. vulgare* Gaertn., *Apium anisum* (L.) Crantz, *Carum anisum* (L.) Baill., *Pimpinella anisum cultum* Alef., *P. aromatica* Bieb., *Selinum anisum* (L.) E.H.L. Krause, *Sison anisum* Spreng., *Tragium anisum* Link (*1, 6–8*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Anacio, Änes, Aneis, anice, anice verde, Anis, anisbibernelle, anis verde, anis vert, anise, anisoon, anisum, ánizs, anizsolaj, annsella, badian, badian rumi, boucage, boucage anis, Grüner Anis, habbat hlawa, jintan manis, jinten manis, petit anis, pimpinelle, razianag, razianaj, roomy, saunf, sweet cumin, yansoon (*1, 6–10*).

Geographical distribution

Indigenous to the eastern Mediterranean region, western Asia and Europe. Cultivated in southern Europe and northern Africa, and in Argentina, Bulgaria, Chile, China, India, Islamic Republic of Iran, Japan, Mexico, Romania, Russian Federation and Turkey (*8*).

Description

An aromatic annual herb, up to 60 cm high with an erect, cylindrical, striated, smooth stem. Leaves alternate below, opposite above, the lower being long-petioled, ovate–orbicular, dentate, the upper with short dilated petioles, pinnatifid or ternately pinnate with long, entire or cut cuneate segments. Inflorescence long-stalked, compound umbel with 8–14 rays; flowers small, white, each on a long hairy pedicel. Fruit comprises a

[1] The *European pharmacopoeia (5)* permits the inclusion of the essential oil of *Illicium verum Hook.*

mouse-shaped cremocarp with a small stylopod and two minutely pubescent mericarps that do not readily separate from the carpophore (*6, 11*).

Plant material of interest: essential oil

General appearance

A clear, colourless or pale yellow liquid, solidifying on cooling, practically insoluble in water, miscible with alcohol, ether, light petroleum or methylene chloride (*1, 5*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet, strongly aromatic (*1*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Thin-layer chromatography for the presence of anethole, anisaldehyde and linalool. A gas chromatography method is also available (*5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Chemical

Soluble in three parts ethanol (90%) at 20 °C (*4*). Relative density 0.978–0.994 (*5*). Refractive index 1.552–1.561 (*5*). Freezing-point 15–19 °C (*5*). Acid value not more than 1.0 (*5*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*13*).

Heavy metals

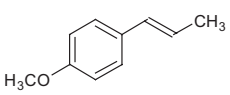
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

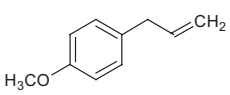
Other purity tests
Tests for foreign organic matter, total ash, acid-insoluble ash, water-soluble extractive, alcohol-soluble extractive and loss on drying not applicable.

Chemical assays
Contains 0.1–1.5% linalool, 0.5–6.0% methylchavicol, 0.1–1.5% α-terpineol, < 0.5% *cis*-anethole, 84–93% *trans*-anethole, 0.1–3.5% *p*-anisaldehyde (*5*).

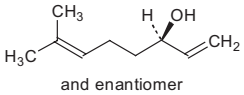
Major chemical constituents
The major constituents are *trans*-anethole (84–93%), *cis*-anethole (< 0.5%), methylchavicol (estragole, isoanethole; 0.5–6.0%), linalool (0.1–1.5%) and *p*-anisaldehyde (0.1–3.5%) (*5*). The structures of *trans*-anethole, methylchavicol, β-linalool and *p*-anisaldehyde are presented below.



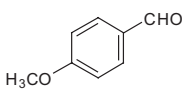
trans-anethole



methylchavicol



β-linalool



p-anisaldehyde

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Treatment of dyspepsia and mild inflammation of the respiratory tract (*14, 15*).

Uses described in traditional medicine
As an aphrodisiac, carminative, emmenagogue, galactagogue and insecticide. Treatment of chronic bronchitis (*8, 10*).

Pharmacology
Experimental pharmacology
Antimicrobial activity
Aetheroleum Anisi, 500 mg/l, inhibited the growth of *Alternaria alternata*, *Alternaria tenuissima*, *Aspergillus* spp., *Botryodiplodia* spp., *Clado-*

sporium herbarum, Cladosporium werneckii, Colletotrichum capsici, Curvularia lunata, Curvularia pallescens, Fusarium moniliforme, F. oxysporum, Mucor spinescens, Penicillium chrysogenum, P. citrinum and *Rhizopus nigricans* (*16*). The oil (concentration not specified) inhibited the growth of *Aspergillus flavus, A. niger, Fusarium oxysporum* and *Penicillium* spp. in vitro (*17*). The oil, 1.0 ml/plate, inhibited the growth of *Rhizoctonia solani* and *Sclerotinia sclerotiorum*, but was inactive against *Fusarium moniliforme* and *Phytophthora capsici* in vitro (*18*). The oil (concentration not specified) did not inhibit the growth of *Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa* or *Staphylococcus aureus* but did inhibit that of *Aspergillus aegyptiacus, Penicillium cyclopium* and *Trichoderma viride* in vitro (*19*). The oil (concentration not specified) was active against *Bacillus subtilis, Escherichia coli, Lentinus lepideus, Pseudomonas aeruginosa* and *Staphylococcus aureus* (*20*). The oil inhibited the growth of *Candida albicans, Candida krusei*, *Candida parapsilosis, Candida tropicalis, Microsporum gypseum, Rhodotorula rubra* and *Saccharomyces cerevisiae*, minimum inhibitory concentration (MIC) 0.097%, and *Geotrichum* spp., MIC 1.562% (*21*).

Anticonvulsant activity

Intraperitoneal administration of 1.0 ml/kg body weight (bw) of the oil to mice suppressed tonic convulsions induced by pentylenetetrazole or maximal electroshock (*22*). Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents provided protection against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*23, 24*). Intraperitoneal administration of 2.5 g/kg bw of linalool to mice interfered with glutamate function and delayed convulsions induced by *N*-methyl-D-aspartate (*25*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes. The effects of linalool were investigated on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes. Linalool, 1.0 mmol/l, reduced potassium-stimulated glutamate release (*26*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity

Anethole is a potent inhibitor of tumour necrosis factor (TNF)-induced nuclear factor (NF)-κβ activation, inhibitor-κβα phosphorylation and degradation, and NF-κβ reporter gene expression in vitro, demonstrating that anethole suppresses inflammation by inhibiting TNF-induced cellular responses (*27*).

Antispasmodic activity
The oil inhibited the phasic contractions of ileal myenteric plexus-longitudinal muscle preparations isolated from guinea-pigs in vitro, median effective dose 60 mg/l (*28*). The oil, 1:20 000, decreased the rate and extent of contractions in intestinal smooth muscle isolated from rats, cats or rabbits in vitro, and antagonized the stimulant activity of acetylcholine, barium chloride, pilocarpine and physostigmine (*29*). Anethole, 0.05–1.00 mg/ml, blocked twitching induced by acetylcholine and caffeine in toad rectus abdominis and sartorius muscles, but had no effect on skeletal muscle twitching induced by nerve stimulation in isolated rat diaphragm (*30*).

Bronchodilatory activity
The oil, 1.0 mmol/l, had relaxant effects in precontracted, isolated guinea-pig tracheal chains indicating a bronchodilatory effect. It also induced a parallel rightwards shift in the methacholine-response curve (methacholine is a muscarinic receptor antagonist), indicating that the bronchodilatory activity may be due to an inhibitory effect of the oil on the muscarinic receptors (*31*).

Estrogenic activity
Subcutaneous administration of 0.1 ml of the oil to ovariectomized rats had an estrogenic effect equivalent to that of 0.1 µg of estradiol (*32*). Intraperitoneal administration of 0.1 ml of the oil had a uterine relaxation effect in female rats (*32*). Anethole is thought to be the estrogenic component of the oil; polymers of this compound, such as dianethole and photoanethole, have also been suggested (*33*).

Expectorant activity
Intragastric administration of 10.0–50.0 mg/kg bw of the oil to guinea-pigs increased bronchial secretions, demonstrating an expectorant effect (*34*). Intragastric administration of two drops of the oil as an emulsion with gummi arabicum to cats induced hypersecretion of the respiratory tract (*35*). However, other researchers have demonstrated that administration of the oil to cats by steam inhalation had no effect on respiratory tract fluid except when given in toxic doses, which increased the output (*36*). Administration of the oil by inhalation to anaesthetized rabbits did not appreciably affect respiratory tract fluids until doses of 720.0 mg/kg bw and over were used in a vaporizer (*36, 37*). At this dose, 20% of the animals died and there was local irritation of the lining of the respiratory tract, which appeared as congestion at 6 hours and progressed to leukocytic infiltration and destruction of the ciliated mucosa at 24 hours (*36*). Inhalation of 1 ml/kg bw of anisaldehyde in anaesthetized rabbits signifi-

cantly increased ($P < 0.05$) the volume of respiratory fluid collected for 4–6 hours after treatment and decreased the specific gravity of the fluid in treated animals compared with untreated controls (*38*).

Liver effects

Subcutaneous administration of 100.0 mg/kg bw of the oil per day for 7 days stimulated liver regeneration in partially hepatectomized rats (*39*).

Toxicology

The oral median lethal dose (LD_{50}) of anisaldehyde in rats was 1.51 g/kg bw, with death occurring within 4–18 hours following depression of the central nervous system (*40*). The oral LD_{50} in guinea-pigs was 1.26 g/kg bw, death occurring after 1–3 days (*40*).

The safety and metabolism of *trans*-anethole were evaluated in rats as a model for assessing the potential for hepatotoxicity in humans exposed to the compound as a flavouring agent. In chronic dietary studies in rats, hepatotoxicity was observed when the estimated daily hepatic production of anethole epoxide exceeded 30 mg/kg bw. Chronic hepatotoxicity and a low incidence of liver tumours were observed at a dietary intake of *trans*-anethole of 550.0 mg/kg bw per day (*41*). The effects of *trans*-anethole on drug metabolizing enzymes were assessed in rats; intragastric administration of 125.0 mg/kg or 250.0 mg/kg bw per day for 10 days had no effect on total cyctochrome P450 content in liver microsomes (*42*). In a chronic feeding study, *trans*-anethole was administered to rats in the diet at concentrations of 0, 0.25%, 0.5% and 1.0% for 117–121 weeks, giving an average dose of 105–550.0 mg/kg bw per day. No abnormalities related to treatment were observed with the exception of a very low incidence of hepatocarcinomas in female animals treated with the 1.0% dose (*43*).

The acute oral LD_{50} of anethole in rats was 2090.0 mg/kg bw; repeated doses of 695.0 mg/kg bw caused mild liver lesions consisting of slight discoloration, mottling and blunting of the lobe edges (*33*).

Clinical pharmacology

The absorption of anethole from the gastrointestinal tract was assessed in healthy volunteers. The drug was rapidly absorbed from the gastrointestinal tract and rapidly eliminated in the urine (54–69%) and through the lungs (13–17%). The principal metabolite was 4-methoxyhippuric acid (approximately 56%); other metabolites were 4-methoxybenzoic acid and three other unidentified compounds (*44, 45*). Increases in drug dose did not alter the pattern of metabolite distribution in humans, contrary to findings in animal models (*46*).

Adverse reactions

Contact dermatitis was reported in a cake factory worker after external exposure to a 5% concentration of Aetheroleum Anisi (*47*). Occasional allergic reactions to the oil affecting the skin, respiratory tract and gastrointestinal tract are reported (*15*). Inhalation of powdered Fructus Anisi induced an allergic effect in one subject with asthma. Skin-prick tests showed a positive reaction to the fruits and the patient had high specific anti-aniseed immunoglobulin E antibodies in his blood (*48*). Anethole toxicity in infants has been reported, and presents clinically with symptoms of hypertonia, continued crying, atypical ocular movements, twitching, cyanosis, vomiting and lack of appetite (*7, 49*). Ingestion of 1.0–5.0 ml of the oil can result in nausea, vomiting, seizures and pulmonary oedema (*50*). In cases of overdose (> 50 mg/kg), the ingestion of milk and alcohol is contraindicated owing to increased resorption.

Contraindications

Aetheroleum Anisi is contraindicated in cases of known allergy to aniseed and anethole (*48*). Owing to the traditional use of the oil as an emmenagogue and to induce labour, its experimental estrogenic and potential mutagenic effects, and reports of anethole toxicity in infants (*7, 49*), use of the oil in pregnancy and nursing, and in children under the age of 12 years is contraindicated.

Warnings

Applications of Aetheroleum Anisi should be limited to inhalation therapy (*51*).

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Inconsistent results have been reported concerning the mutagenicity of *trans*-anethole in the *Salmonella*/microsome assay. One group showed that anethole was mutagenic (*52*), another that it was very weakly mutagenic in *S. typhimurium* strains TA1535, TA100 and TA98 (*53*). In a further study, *trans*-anethole (concentrations not specified) did not increase the mutant frequency in the *Salmonella*/microsome assay, but did increase mutant frequency in the L5178Y mouse-lymphoma TK+/- assay in a dose-dependent manner, with metabolic activation (*49*). *Trans*-anethole did not induce chromosome aberrations in vitro in the Chinese hamster ovary cell assay (*49*). *Trans*-anethole was weakly hepatocarcinogenic in female rats when administered at a dose of 1% in the diet for 121 weeks;

however, this effect is not mediated by a genotoxic event (*54*). *Trans*-anethole was investigated for its antifertility activity in rats, after intragastric administration of doses of 50.0 mg/kg bw, 70.0 mg/kg bw and 80.0 mg/kg bw (*55*). Anti-implantation activity of 100% was observed in animals treated with the highest dose. The compound has been reported to show estrogenic, antiprogestational, androgenic and antiandrogenic activities (*55*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; and teratogenic effects in pregnancy.

Dosage forms
Essential oil. Preparations containing 5–10% essential oil for inhalation are also available. Store in a well-filled, tightly sealed container, protected from light and heat (*5*).

Posology
(Unless otherwise indicated)
Average daily dose for internal use: essential oil 0.3 g; equivalent for other preparations (*15*).

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Fructus Anisi

Definition

Fructus Anisi consists of the dried fruits of *Pimpinella anisum* L. (Apiaceae) (*1–3*).

Synonyms

Anisum officinarum Moench, *A. vulgare* Gaertn., *Apium anisum* (L.) Crantz, *Carum anisum* (L.) Baill., *Pimpinella anisum cultum* Alef., *P. aromatica* Bieb., *Selinum anisum* (L.) E.H.L. Krause, *Sison anisum* Spreng., *Tragium anisum* Link (*1, 2, 4, 5*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Anacio, Änes, Aneis, anice, anice verde, Anis, anisbibernelle, anis verde, anis vert, anise, anisoon, anisum, ánizs, anizsolaj, annsella, badian, badian rumi, boucage, boucage anis, Grüner Anis, habbat hlawa, jintan manis, jinten manis, petit anis, pimpinelle, razianag, razianaj, roomy saunf, sweet cumin, yansoon (*1, 2, 4–7*).

Geographical distribution

Indigenous to the eastern Mediterranean region, western Asia and Europe. Cultivated in southern Europe and northern Africa, and in Argentina, Bulgaria, Chile, China, India, Islamic Republic of Iran, Japan, Mexico, Romania, Russian Federation and Turkey (*5, 8*).

Description

An aromatic annual herb, up to 60 cm high, with an erect, cylindrical, striated, smooth stem. Leaves alternate below, opposite above, the lower being long-petioled, ovate–orbicular, dentate, the upper with short, dilated petioles, pinnatifid or ternately pinnate with long, entire or cut cuneate segments. Inflorescence long-stalked, compound umbel with 8–14 rays; flowers small, white, each on a long hairy pedicel. Fruit comprises a mouse-shaped cremocarp with a small stylopod and two minutely pubescent mericarps that do not readily separate from the carpophore (*2, 9*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp, partly separated into its mericarps, often entire, remaining attached to a slender pedicel 2–12 mm long; pear-shaped, 3–6 mm long and 2–3 mm wide, enlarged at the base and tapering at the apex, somewhat laterally compressed, crowned with a disc-like nectary; stylopod ends with the remains of two diverging styles; greyish or greenish-grey, seldom greyish-brown. Mericarp externally rough to the touch owing to the presence of numerous very short, stiff hairs; marked with five very slightly raised, filiform, pale-brown primary ridges; commissural surface, nearly flat, with two dark brownish, longitudinal areas, containing vittae, separated by a middle paler area; internally comprises a pericarp with numerous branched vittae in the dorsal side and usually only two large ones in the commissural side, a large white oily endosperm, not deeply grooved on the commissural side, and a small apical embryo. Carpophore forked, passing at the apex into the raphe of each pericarp (*1, 2*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet, strongly aromatic (*1, 2*).

Microscopic characteristics

Pericarp epidermis consists of cells with striated cuticle, many of which project into short, conical, curved, thick-walled, unicellular, sometimes bicellular, non-glandular hairs, with bluntly pointed apex and finely warty cuticles. Mesocarp formed of thin-walled parenchyma, traversed longitudinally by numerous schizogenous vittae, with brown epithelial cells and, in each primary ridge, by a small vascular bundle, accompanied by a few fibres; also a patch of porous or reticulate lignified cells in the middle of the commissural side, but not in the ridges. Endocarp composed of narrow, tangentially elongated, thin-walled cells, except when adjacent to the reticulate cells in the mesocarp, where it is formed of porous, lignified and reticulately thickened cells. Testa consists of one layer of tangentially elongated cells with yellowish-brown walls, closely adhering to the endocarp except along the commissural surface, where separated by a large cavity. Endosperm formed of polygonal thick-walled cellulosic cells containing fixed oil and many aleurone grains, each enclosing one globoid and one or two microrosette crystals of calcium oxalate with dark centres. Carpophore traversed by a vascular bundle of fibres and spiral vessels (*1, 2*).

Powdered plant material

Grey, greenish-brown or yellowish-brown, characterized by numerous, almost colourless fragments of endosperm; abundant minute oil globules; numerous warty simple hairs 25–100 µm long and 10–15 µm wide. Fragments of pericarp with yellowish-brown, comparatively narrow, branching vittae, usually crossed by the cells of the endocarp, the ratio of the width of these cells to that of the vittae varying from 1:7 to 1:5. Few fibres and very scanty pitted lignified parenchyma; aleurone grains 2–15 µm in diameter. Microrosette crystals of calcium oxalate 2–10 µm in diameter, each containing a minute air bubble (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations (*2*, *3*), and thin-layer chromatography for the presence of anethole (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 2.0% (*3*).

Total ash

Not more than 12.0% (*3*).

Acid-insoluble ash

Not more than 2.5% (*1*, *3*).

Loss on drying

Not more than 7.0% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*11*).

Heavy metals

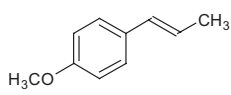
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

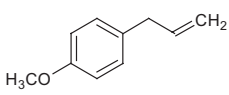
Other purity tests
Chemical, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 2% (v/w) essential oil (*3*). A high-performance liquid chromatography method for the analysis of phenylpropanoid constituents is available (*12*).

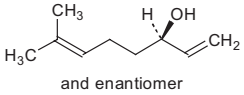
Major chemical constituents
Contains 1.5–5.0% essential oil, the major constituents of which are linalool (0.1–1.5%), methylchavicol (estragole, isoanethole; 0.5–6.0%), α-terpineol (0.1–1.5%), *cis*-anethole (< 0.5%), *trans*-anethole (84–93%), *p*-anisaldehyde (0.1–3.5%) (*3*). The structures of *trans*-anethole, methylchavicol, β-linalool and *p*-anisaldehyde are presented below.



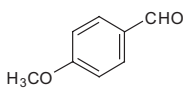
trans-anethole



methylchavicol



β-linalool



p-anisaldehyde

Medicinal uses
Uses supported by clinical data
No information available.

Uses described in pharmacopoeias and well established documents
Treatment of dyspepsia and mild inflammation of the respiratory tract (*13, 14*).

Uses described in traditional medicine
As an aphrodisiac, carminative, emmenagogue, galactagogue and tonic, and for treatment of asthma, bronchitis, diarrhoea, fever, spasmodic cough, flatulent colic and urinary tract infections (*5, 7, 15*).

Pharmacology
Experimental pharmacology
Analgesic and central nervous system activity
Intraperitoneal or intragastric administration of a dried ether extract of the fruits dissolved in normal saline did not potentiate barbiturate-

induced sleeping time when administered to mice in doses of up to 200.0 mg/kg body weight (bw) (*16*).

Antimicrobial activity

A 95% ethanol extract of the fruits, 50 µl/plate, inhibited the growth of *Staphylococcus aureus* in vitro (*17*). A dried methanol extract of the fruits inhibited the growth of *Helicobacter pylori* in vitro, minimum inhibitory concentration (MIC) 100.0 µg/ml (*18*). A decoction of the fruits did not inhibit the growth of *Aspergillus niger, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi* or *Staphylococcus aureus* in vitro at concentrations of up to 62.5 mg/ml (*19*). An ethanol extract of the fruits inhibited the growth of *Candida albicans, C. krusei, C. parapsilosis, C. tropicalis, Microsporum gypseum, Rhodotorula rubra* and *Saccharomyces cerevisiae*, MIC 0.097%, and *Geotrichum* spp., MIC 1.562% (*20*).

Anticonvulsant activity

Intraperitoneal administration of 4.0 mg/kg bw of a dried 95% ethanol extract of the fruits dissolved in normal saline to mice inhibited convulsions induced by supramaximal electroshock. At the same dose, the extract was ineffective against convulsions induced by pentylenetetrazole and strychnine (*21*).

Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents provided protection against convulsions induced by pentylenetetrazole, picrotoxin, and electroshock (*22, 23*). Intraperitoneal administration of 2.5 g/kg bw of linalool to mice interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*24*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool, 1.0 mmol/l, reduced potassium-stimulated glutamate release (*25*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity

External application of 2.0 mg of a methanol extract of the fruits inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate in mice (*26*). External application of 20.0 µl of an ethyl acetate or hexane extract of the fruits did not inhibit ear inflammation induced by *O*-tetradecanoylphorbol-13-acetate in mice; application of 20.0 µl of a methanol extract was weakly active in the same assay (*27*). Anethole is a potent inhibitor of tumour necrosis factor (TNF)-induced nuclear factor (NF)-κβ activation, inhibitor-κβα phosphorylation and degradation, and

NF-κβ reporter gene expression in vitro, demonstrating that anethole suppresses inflammation by inhibiting TNF-induced cellular responses (*28*).

Bronchodilatory activity

The fruits, 1.0 mmol/l, had significant ($P < 0.05$) relaxant effects in precontracted, isolated guinea-pig tracheal chains in vitro, indicating a bronchodilatory effect. At the same dose, the fruits induced a parallel rightwards shift in the methacholine-response curve, indicating that the bronchodilatory activity may be due to an inhibitory effect on the muscarinic receptors (*29*).

Hypotensive activity

Intravenous administration of 50.0 mg/kg bw of a dried 50% ethanol extract of the fruits dissolved in normal saline to dogs decreased blood pressure (*30*). Intragastric administration of an aqueous extract of the fruits reduced atropine-induced hypertension at a dose of 10.0% (no further information available) (*31*). Administration of an unspecified extract of the fruits had a diuretic effect in rabbits, which was blocked by pretreatment with morphine (*32*).

Platelet aggregation inhibition

A methanol extract of the fruits, 500.0 µg/ml, inhibited collagen-induced platelet aggregation in human platelets (*33*).

Smooth muscle stimulant activity

An aqueous extract of the fruits, 10.0% in the bath medium, stimulated contractions of isolated frog rectus abdominis muscle and rat jejunum strips (*31*). Anethole, 0.05–1.00 mg/ml, blocked twitching induced by acetylcholine and caffeine in toad rectus abdominis and sartorius muscles, but had no effect on skeletal muscle twitching in isolated rat diaphragm induced by electrical nerve stimulation (*34*).

Toxicity

For intraperitoneal injection of a dried 50% ethanol extract of the fruits dissolved in normal saline in mice, the maximum tolerated dose was 500.0 mg/kg bw, median lethal dose (LD_{50}) 750.0 mg/kg (*30*).

The safety and metabolism of *trans*-anethole were evaluated in rats as a model for assessing the potential for hepatotoxicity in humans exposed to the compound as a flavouring agent. In chronic dietary studies in rats, hepatotoxicity was observed when the estimated daily hepatic production of anethole epoxide exceeded 30.0 mg/kg bw. Chronic hepatotoxicity and a low incidence of liver tumours were observed at a dietary intake of *trans*-anethole of 550.0 mg/kg bw per day (*35*). The effects of *trans*-anethole on

drug-metabolizing enzymes were assessed in rats; intragastric administration of 125.0 mg/kg bw or 250.0 mg/kg bw per day for 10 days had no effect on total cyctochrome P450 content in liver microsomes (*36*). In a chronic feeding study, *trans*-anethole was administered to rats in the diet at concentrations of 0, 0.25%, 0.5% and 1.0% for 117–121 weeks, giving an average dose of 105–550.0 mg/kg bw per day. No abnormalities related to treatment were observed, with the exception of a very low incidence of hepatocarcinomas in female animals treated with the 1.0% dose (*37*).

The acute oral LD_{50} for anethole in rats was 2.09 g/kg bw; repeated oral doses of 695.0 mg/kg bw caused mild liver lesions consisting of slight discoloration, mottling, and blunting of the lobe edges (*38*).

Clinical pharmacology

No information available.

Adverse reactions

Occasional allergic reactions to Fructus Anisi affecting the skin, respiratory tract and gastrointestinal tract have been reported (*14*). Inhalation of powdered fruits induced an allergic effect in one subject with asthma. Skin-prick tests showed a positive reaction and the patient had a high level of specific anti-aniseed immunoglobulin E antibodies in his blood (*39*). Anethole toxicity in infants has been reported, and presents clinically with symptoms of hypertonia, continued crying, atypical ocular movements, twitching, cyanosis, vomiting and lack of appetite (*4, 40*).

Contraindications

Fructus Anisi is contraindicated in cases of known allergy to aniseed and anethole (*14, 39*). Owing to the traditional use of the oil as an emmenagogue and to induce labour, its experimental estrogenic and potential mutagenic effects, and reports of anethole toxicity in infants (*4, 40*), use of the dried fruits in pregnancy and nursing, and in children under the age of 12 years is contraindicated.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Anisi, 10.0 mg/plate, was inactive in the *Salmonella*/microsome assay in *S. typhimurium* TA102 (*41*). Inconsistent

results have been reported concerning the mutagenicity of anethole in this assay. One group showed that it was mutagenic (*42*), another that it was not mutagenic in *S. typhimurium* strains TA1535, TA100 and TA98 (*43*). In a further study, *trans*-anethole (concentration not specified) did not increase the mutant frequency in the *Salmonella*/microsome assay, but did increase mutant frequency in the L5178Y mouse-lymphoma TK+/- assay in a dose-dependent manner, with metabolic activation (*40*). *Trans*-anethole did not induce chromosome aberrations in vitro in the Chinese hamster ovary cell assay (*40*). *Trans*-anethole was weakly hepatocarcinogenic in female rats when administered at a dose of 1% in the diet for 121 weeks; however, this effect is not mediated by a genotoxic event (*44*). *Trans*-anethole was investigated for its antifertility activity in rats, after intragastric administration of doses of 50.0 mg/kg bw, 70.0 mg/kg bw and 80.0 mg/kg bw (*45*). Anti-implantation activity of 100% was observed in animals treated with the highest dose. The compound has been reported to show estrogenic, antiprogestational, androgenic and antiandrogenic activities (*45*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms

Powdered dried fruits for oral infusions and other galenical preparations for internal use or inhalation (*14*). Store in a well-closed container, protected from heat and light.

Posology

(Unless otherwise indicated)
Average oral daily dose for internal use: Fructus Anisi 3.0 g; equivalent for other preparations (*14*).

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Semen Armeniacae

Definition

Semen Armeniacae consists of the dried ripe seeds of *Prunus armeniaca* L., *Prunus armeniaca* L. var. *ansu* Maxim. or allied species (Rosaceae) (*1–4*).

Synonyms

Armeniaca vulgaris Lam. (*5*).

Selected vernacular names

Abricotier, anzu, apricot, Aprikose, Aprikosenbaum, barqouq, bitter apricot, chuli, cuari, culu, elk mesmas, haeng-in, Himalayan wild apricot, hsing, ku-xinggren, kurbani, maó, michmich, mouchmouch, ó mai, sal-goo, touffah armani, wild apricot, xing ren, zardalou, zardalu (*3, 5–8*).

Geographical distribution

Indigenous to the Korean peninsula and to China, India and Japan (*9, 10*). Cultivated in Asia, North Africa and United States of America (*11*).

Description

A medium-sized, deciduous tree, with reddish bark and glabrous twigs. Leaves convoluted in bud, blade broadly ovate, 5–7 cm long, 4–5 cm wide, acuminate, crenate-glandular, hairy on the veins of the underside when young, glabrous when mature, except for the axils of the underside veins. Petiole approximately 2.5 cm long, glandular; stipules, lanceolate, glandular on the margins. Flowers appearing before the leaves, bisexual, pinkish to white, solitary or fascicled, pedicels very short; calyx-tube campanulate, puberulent, 5 mm long; surrounding lobes, pubescent, half the length of the tube; petals suborbicular, 7–13 mm long; stamens inserted with the petals at the mouth of the calyx-tube; ovary and base of the style hairy. Fruit a downy or glabrous, yellow-tinged, red drupe with a fleshy outer layer surrounding a hard stone containing the seed (*9, 10*).

Plant material of interest: dried ripe seeds

General appearance

Flattened, cordate, 1.1–1.9 cm long, 0.8–1.5 cm wide, 0.4–0.8 cm thick, acute at one end, plump, unsymmetrical, rounded at the other. Seed coat yellowish-brown to deep brown; short linear hilum situated at the acute end; chalaza at the rounded end, with numerous, deep-brown veins radiating upwards. Testa, thin; two cotyledons (*1, 3, 4*).

Organoleptic properties

Odourless; taste: bitter (*1, 3, 4*).

Microscopic characteristics

Epidermal surface has stone cells, 60–90 µm in diameter, on veins protruded by vascular bundles, which appear as angular circles–ellipses, approximately uniform in shape, with uniformly thickened walls. In lateral view, stone cells appear obtusely triangular, walls extremely thickened at the apex (*1, 2*).

Powdered plant material

See characteristic features under Microscopic characteristics (*1, 2*).

General identity tests

Macroscopic and microscopic examinations, and microchemical tests (*1, 2, 4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

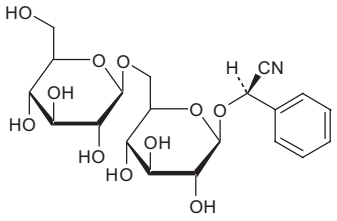
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, alcohol-soluble extractive, water-soluble extractive and loss on drying tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 3.0% amygdalin determined by titrimetric assay with silver nitrate (*4*). A high-performance liquid chromatography method is also available (*15*).

Major chemical constituents
The major constituent is amygdalin (up to 4.9%), a cyanogenic glycoside (a plant compound that contains sugar and produces cyanide). Other cyanogenic compounds present are prunasin and mandelonitrile. Also present are the amygdalin-hydrolysing enzyme, emulsin, and fatty acids and sitosterols (*8, 16*). The structure of amygdalin is presented below.

amygdalin



Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Internally as a decoction, after processing by dipping in boiling water and stir-frying until yellow (*4*), for symptomatic treatment of asthma, cough with profuse expectoration and fever. The seed oil is used for treatment of constipation (*3, 4*).

Uses described in traditional medicine
Treatment of gynaecological disorders, skin hyperpigmentation, headache and rheumatic pain (*8*). The seed oil is used in the form of eardrops for inflammation and tinnitus, and for treatment of skin diseases (*17*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activity

Intragastric administration of 46.32 mg/kg body weight (bw) of amygdalin to rats induced a small increase in body temperature, and prevented ephedrine-induced hyperthermia (*18*). In the hot plate and acetic acid-induced writhing tests in mice, the analgesic median effective doses (ED_{50}) were 457.0 mg/kg and 288.0 mg/kg bw, respectively. However, at these doses, amygdalin could not substitute for morphine in morphine-addicted rats in relieving withdrawal syndrome. No anti-inflammatory effects were observed in the animals treated with amygdalin (*19*).

Antitumour activity

Intragastric administration of 200.0 mg/kg–2.0 g/kg bw of amygdalin to mice with P388 lymphocytic leukaemia or P815 mast-cell leukaemia on days 1 and 5, or days 1, 5 and 9. Despite treatment with high doses of amygdalin there was no prolongation in the lifespan of mice in either group (*20*).

Antitussive activity

Amygdalin, 30.0 mg, had antitussive effects in the sulfur dioxide gas-induced cough model in mice (*21, 22*). The enzymes amygdalase and prunase, along with gastric juice, hydrolyse amygdalin to form small amounts of hydrocyanic acid, thereby stimulating the respiratory reflex and producing antitussive and antiasthmatic effects (*19*).

Metabolism and pharmacokinetics

After intragastric administration of 30.0 mg of amygdalin or prunasin to rats, capacity for hydrolysing these compounds was greatest in the organs of 15-day-old animals, most of the activity being concentrated in the tissues of the small and large intestines. The activity decreased with age. In adult rats, hydrolysis of prunasin was greater than that of amygdalin and was concentrated in the spleen, large intestine and kidney (35.0 µg, 15.0 µg and 8.9 µg of prunasin hydrolysed per hour per gram of tissue, respectively). Minced liver, spleen, kidney and stomach tissue had a greater hydrolytic capability than the homogenate of these organs, while the reverse was the case with the small and large intestines. Following oral administration of 30.0 mg of amygdalin to adult rats, distribution after the first hour was as follows: stomach 0.89 mg, small intestine 0.78 mg, spleen 0.36 mg, large intestine 0.30 mg, kidney 0.19 mg, liver 0.10 mg and serum 5.6 µg/ml. At the end of the second hour, the highest amygdalin content, 0.79 mg, was found in the large intestine (*23, 24*).

Toxicology

Intragastric administration of 125.0 mg/kg bw of powdered defatted Semen Armeniacae per day for 7 days to mice or rabbits produced no behavioural, histological or microscopic toxic effects (*25*). Intragastric administration of 250.0 mg/kg bw of an aqueous suspension of the powdered defatted seeds to mice had no toxic effects within a 24-hour period (*25*). The median lethal dose (LD_{50}) of amygdalin in rats was 880.0 mg/kg bw after intragastric administration. However, when a dose of 600.0 mg/kg bw was administered by the same route, together with β-glucosidase, all animals died. Total and magnesium adenosine triphosphatase activities in the heart decreased with increasing levels of administered amygdalin (*23, 24*).

Diets containing 10% ground seeds were fed to young and breeding male and female rats. The seeds were obtained from 35 specific apricot cultivars and divided into groups containing low amygdalin (cyanide < 50.0 mg/100 g), moderate amygdalin (cyanide 100–200.0 mg/100 g), or high amygdalin (cyanide > 200.0 mg/100 g). Growth of young male rats was greatest in the low and moderate amygdalin groups, indicating that the animals were more sensitive to the bitter taste of the kernels with high amygdalin content. In female rats, but not males, liver rhodanase activity and blood thiocyanate levels were increased with the high-amygdalin diet, but both males and females efficiently excreted thiocyanate, indicating efficient detoxification and clearance of cyanide hydrolysed from the dietary amygdalin. No other changes in blood chemistry were observed (*26*).

Toxic amounts of cyanide were released into the blood of rats following intragastric administration of amygdalin (proprietary laetrile) (dose not specified); cyanide blood concentrations and toxicity were lower when amygdalin was given intravenously (dose not specified). Analysis of the time course of cyanogenesis suggests that cyanide could accumulate in blood after repeated oral doses of amygdalin (*27*). Following intraperitoneal administration of 250.0 mg/kg bw, 500.0 mg/kg bw or 750.0 mg/kg bw of amygdalin per day to rats for 5 days, mortalities were 30.8%, 44.1% and 56.8%, respectively. The mode of death and the elevated serum cyanide levels in the dying animals strongly suggested cyanide poisoning as the cause of death (*28*).

The systemic effects of an oil prepared from the seeds containing 94% unsaturated fatty acids, and oleic and linoleic acids were assessed in a 13-week feeding study in rats. The animals were fed a diet containing 10% oil. No toxic effects were observed and no macroscopic or microscopic lesions in any of the organs were found (*29*). External applications of 0.5 ml of the seed oil to rabbits did not produce any observable toxic effects (*25*).

Clinical pharmacology

Antitumour activity

The term "laetrile" is an acronym used to describe a purified form of amygdalin, a cyanogenic glucoside found in the pits of many fruits and raw nuts and in other plants, such as lima beans, clover and sorghum (*30*). However, the chemical composition of a proprietary laetrile preparation patented in the United States of America (Laetrile®), which comprises mandelonitrile-β-glucuronide, a semisynthetic derivative of amygdalin, is different from that of natural laetrile/amygdalin, which consists of mandelonitrile β-D-gentiobioside and is made from crushed apricot pits. Mandelonitrile, which contains cyanide, is a structural component of both products. It has been proposed that the cyanide is an active anticancer ingredient in laetrile, but two other breakdown products of amygdalin, prunasin (which is similar in structure to the proprietary product) and benzaldehyde, have also been suggested. The studies discussed in this summary used either Mexican laetrile/amygdalin or the proprietary formulation. Laetrile can be administered orally as a pill, or it can be given by injection (intravenous or intramuscular). It is commonly given intravenously over a period of time followed by oral maintenance therapy. The incidence of cyanide poisoning is much higher when laetrile is taken orally because intestinal bacteria and some commonly eaten plants contain enzymes (β-glucosidases) that activate the release of cyanide following laetrile ingestion (*31*). Relatively little breakdown to yield cyanide occurs when laetrile is injected (*32*).

Laetrile has been used as an anticancer treatment in humans worldwide. While many anecdotal reports and case reports are available, results from only two clinical trials have been published (*33, 34*). No controlled clinical trial (a trial including a comparison group that receives no additional treatment, a placebo, or another treatment) of laetrile has ever been conducted. Case reports and reports of case series have provided little evidence to support laetrile as an anticancer treatment (*35*). The absence of a uniform documentation of cancer diagnosis, the use of conventional therapies in combination with laetrile, and variations in the dose and duration of laetrile therapy complicate evaluation of the data. In a published case series, findings from ten patients with various types of metastatic cancer were reported (*36*). These patients had been treated with a wide range of doses of intravenous proprietary laetrile (total dose range 9–133 g). Pain relief (reduction or elimination) was the primary benefit reported. Some responses, such as decreased adenopathy (swollen lymph nodes) and decreased tumour size, were noted. Information on prior or concurrent therapy was provided; however, patients were not followed

long-term to determine whether the benefits continued after treatment ceased. Another case series, published in 1953, included 44 cancer patients and found no evidence of objective response that could be attributed to laetrile (*37*). Most patients with reported cancer regression in this series had recently received or were receiving concurrent radiation therapy or chemotherapy. Thus, it is impossible to determine which treatment produced the positive results.

In 1978, the United States National Cancer Institute (NCI), at the National Institutes of Health, requested case reports from practitioners who believed their patients had benefited from laetrile treatment (*38*). Of the 93 cases submitted, 67 were considered suitable for evaluation. An expert panel concluded that only two of the 67 patients had complete responses, and that four others had partial responses while using laetrile. On the basis of these six responses, NCI agreed to sponsor phase I and phase II clinical trials. The phase I study was designed to test the doses, routes of administration and schedule of administration. Six patients with advanced cancer were treated with amygdalin given intravenously at 4.5 g/m^2 per day. The drug was largely excreted unchanged in the urine and produced no clinical or laboratory evidence of a toxic reaction. Amygdalin given orally, 0.5 g three times daily, produced blood cyanide levels of up to 2.1 µg/ml. No clinical or laboratory evidence of toxic reaction was seen in the six patients taking the drug at this dosage. However, two patients who ate raw almonds while undergoing oral treatment developed symptoms of cyanide poisoning (*33*).

In the phase II clinical trial, 175 patients with various types of cancer (breast, colon, lung) were treated with amygdalin plus a "metabolic therapy" programme consisting of a special diet, with enzymes and vitamins. The great majority of these patients were in good general condition before treatment. None was totally disabled or in a preterminal condition. One-third had not received any previous chemotherapy. The amygdalin preparations were administered by intravenous injection for 21 days, followed by oral maintenance therapy, dosages and schedules being similar to those evaluated in the phase I study. Vitamins and pancreatic enzymes were also administered as part of a metabolic therapy programme that included dietary changes to restrict the use of caffeine, sugar, meats, dairy products, eggs and alcohol. A small subset of patients received higher-dose amygdalin therapy and higher doses of some vitamins as part of the trial. Patients were followed until there was definite evidence of cancer progression, elevated blood cyanide levels or severe clinical deterioration. Among 175 patients suitable for assessment, only one met the criteria for response. This patient, who had gastric carcinoma with cervical lymph

node metastasis, experienced a partial response that was maintained for 10 weeks while on amygdalin therapy. In 54% of patients there was measurable disease progression at the end of the intravenous course of treatment, and all patients had progression 7 months after completing intravenous therapy; 7% reported an improvement in performance status (ability to work or to perform routine daily activities) at some time during therapy, and 20% claimed symptomatic relief. In most patients, these benefits did not persist. Blood cyanide levels were not elevated after intravenous amygdalin treatment; however, they were elevated after oral therapy (*34*). On the basis of this phase II study, NCI concluded that no further investigation of laetrile was warranted.

Adverse reactions

The side-effects associated with amygdalin treatment are the same as the symptoms of cyanide poisoning. Cyanide is a neurotoxin that initially causes nausea and vomiting, headache and dizziness, rapidly progressing to cyanosis (bluish discoloration of the skin due to oxygen-deprived haemoglobin in the blood), liver damage, marked hypotension, ptosis (droopy upper eyelid), ataxic neuropathies (difficulty in walking due to damaged nerves), fever, mental confusion, convulsions, coma and death. These side-effects can be potentiated by the concurrent administration of raw almonds or crushed fruit pits, eating fruits and vegetables that contain β-glucosidase, such as celery, peaches, bean sprouts and carrots, or high doses of vitamin C (*35*).

Numerous cases of cyanide poisoning from amygdalin have been reported (*39–42*). After ingestion, amygdalin is metabolized in the gastrointestinal tract to produce prunasin and mandelonitrile, which are further broken down to benzaldehyde and hydrocyanic acid, the latter of which is highly toxic. Overdose causes dizziness, nausea, vomiting and headache, which may progress to dyspnoea, spasms, dilated pupils, arrhythmias and coma. A 65-year-old woman with cirrhosis and hepatoma lapsed into deep coma, and developed hypotension and acidosis after ingestion of 3 g of amygdalin. After initial treatment, the patient regained consciousness, but massive hepatic damage led to her death (*42*). A 67-year-old woman with lymphoma suffered severe neuromyopathy following amygdalin treatment, with elevated blood and urinary thiocyanate and cyanide levels. Sural nerve biopsy revealed a mixed pattern of demyelination and axonal degeneration, the latter being prominent. Gastrocnemius muscle biopsy showed a mixed pattern of denervation and myopathy with type II atrophy (*41*).

Contraindications

Semen Armeniacae should not be administered during pregnancy or nursing, or to children (*43*, *44*).

Warnings

Overdose may cause fatal intoxication (*4*, *43*, *44*). The lethal dose is reported to be 7–10 kernels in children and 50–60 kernels (approximately 30 g) in adults (*45*).

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No effects on fertility were observed in rats fed a diet containing 10% Semen Armeniacae for 5 weeks (*26*). An aqueous extract of the seeds was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, or in the *Bacillus subtilis* H-17 recombinant assay at concentrations of up to 100.0 mg/ml (*46*). However, a hot aqueous extract of the seeds was mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 at a concentration of 12.5 mg/plate (*47*).

Pregnancy: teratogenic effects

Intragastric administration of amygdalin (dose not specified) to pregnant hamsters induced skeletal malformations in the offspring, and intravenous administration resulted in embryopathic effects. Oral laetrile increased in situ cyanide concentrations, while intravenous laetrile did not. Thiosulfate administration protected embryos from the teratogenic effects of oral laetrile. The embryopathic effects of oral laetrile appear to be due to cyanide released by bacterial β-glucosidase activity (*48*). A pregnant woman who took laetrile as daily intramuscular injections (dose not specified) during the last trimester gave birth to a live infant at term. There was no laboratory or clinical evidence of elevated cyanide or thiocyanate levels (*49*).

Pregnancy: non-teratogenic effects

Offspring of breeding rats fed a high-amygdalin diet (cyanide > 200.0 mg/100 g) for 18 weeks had lower 3-day survival indices, lactation indices and weaning weights than those in a low-amygdalin group (cyanide < 50.0 mg/100 g). This may indicate that the cyanide present in the milk may not be efficiently detoxified to thiocyanate and excreted by neonates (*26*).

Nursing mothers

See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Processed (see Posology) dried ripe seeds (*4*); seed oil. Store in a cool, dry place, protected from moths (*4*).

Posology
(Unless otherwise indicated)
Average daily dose: 3.0–9.0 g of dried ripe seeds processed by breaking into pieces, rinsing in boiling water and stir-frying until yellow, then adding to a decoction when nearly finished (*4*).

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Flos Arnicae

Definition
Flos Arnicae consists of the dried flower heads (capitula) of *Arnica montana* L. (Asteraceae) (*1–3*).

Synonyms
Doronicum arnica Desf., *D. montanum* Lam. (*4*). Asteraceae are also known as Compositae.

Selected vernacular names
Arnica, arnika, arnique, bétoine des montagnes, betouana, Bergwohlverleih, celtic bane, dokhanolfouh, Echtes Wolferlei, estourniga, estrunica, Fallkraut, Kraftwurz, leopard's bane, mountain arnica, mountain tobacco, St Luzianskraut, Stichwurzel, strunica, Verfangkraut, Wohlverleih, wolf's bane, Wundkraut (*4–9*).

Geographical distribution
Indigenous to central Europe. Widely cultivated around the world (*1, 4, 7*).

Description
A perennial herb, 20–50 cm high. Aerial portion consists of a basal rosette of entire oblanceolate leaves up to 17 cm long, five to seven veins, from the centre of which projects an erect, simple, glandular hairy stem up to 0.6 m high. Stem bears two to four pairs of cauline leaves, ovate, elliptic-oblong, lanceolate or oblanceolate, with rounded or rounded-toothed apex and clothed with numerous nonglandular and glandular hairs, up to 16 cm long and 5 cm wide. Peduncles, one to three, bearing alternate bracteoles, extending from the uppermost pair of cauline leaves; glandular–puberulent, each terminating in a hemispherical or turbinate capitulum bearing orange-yellow flowers, which are tubular. Fruits, black to brown, five-ribbed, with a bristle tuft of hairs (*5, 8*).

Plant material of interest: dried flower heads

General appearance

Capitulum about 20 mm in diameter and 15 mm deep, with a peduncle 2–3 cm long. Involucre with 18–24 elongated lanceolate bracts, 8–10 mm long with acute apices, arranged in one or two rows, green with yellowish-green external hairs visible under a lens. Receptacle, about 6 mm in diameter, convex, alveolate and covered with hairs; periphery bears about 20 ligulate florets 20–30 mm long; disc bears a greater number of tubular florets about 15 mm long. Ovary, 4–8 mm long, crowned by a pappus of whitish bristles 4–8 mm long. Some brown achenes, crowned or not by a pappus, may be present (*3*).

Organoleptic properties

Odour: characteristic aromatic (*1, 3, 5*); taste: bitter and acrid (*1, 5*).

Microscopic characteristics

Epidermis of corolla papillose, containing yellow-orange globular masses, some cells also containing dark brown–black patches of phytomelan; base of corolla tube of ligulate florets with uniseriate covering trichomes of four to six cells, up to 1 mm in length; bristles of pappus four to six cells in diameter and barbed by exertion of the pointed cell apices. Cells of ovary or fruit walls contain abundant black patches of phytomelan. Corolla and ovary wall with numerous composite glandular trichomes; ovary wall with numerous appressed twin hairs each composed of two narrow parallel cells diverging at the tips. Pollen grains spiky, spherical 35–52 µm in diameter, with finely granular exine, spines up to 8 µm long, three pores and furrows (*1*).

Powdered plant material

Light yellowish-brown to light olive-brown. Epidermis of the involucre bracts with stomata and trichomes, which are more abundant on the outer surface. Trichomes include: uniseriate multicellular covering trichomes, 50–500 µm long, particularly abundant on the margins; secretory trichomes about 300.0 µm long with uni- or biseriate multicellular stalks and with multicellullar, globular heads, abundant on the outer surface; similar trichomes, 80.0 µm long, abundant on the inner surface of the bract. Epidermis of the ligulate corolla consists of lobed or elongated cells, a few stomata and trichomes of different types: covering trichomes, with very sharp ends, whose length may exceed 500 µm; secondary trichomes with multicellular stalks and multicellular globular heads. Ligule ends in rounded papillose cells. Epidermis of the ovary covered with trichomes: secondary trichomes with short stalks and multicellular globular

heads; twinned covering trichomes usually consisting of two longitudinally united cells, with common punctuated walls, their ends sharp and sometimes bifid. Epidermis of the calyx consists of elongated cells bearing short, unicellular, covering trichomes pointing towards the upper end of the bristle. Pollen grains, about 30 µm in diameter, rounded, with spiny exine, and three germinal pores (*3*).

General identity tests

Macroscopic and microscopic examinations (*1*, *3–5*), and thin-layer chromatography for phenolic compounds (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 5.0% (*3*).

Total ash

Not more than 10% (*3*).

Acid-insoluble ash

Not more than 1.2% (*11*).

Sulfated ash

Not more than 13% (*2*).

Water-soluble extractive

Not less than 17% (*2*).

Alcohol-soluble extractive

Not less than 15% using 45% ethanol (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European Pharmacopoeia*

(*12*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Chemical tests to be established in accordance with national requirements.

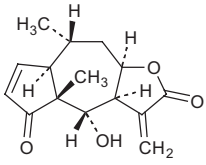
Chemical assays

Contains not less than 0.40% of total sesquiterpene lactones calculated as helenalin tiglate, determined by high-performance liquid chromatography (*3*).

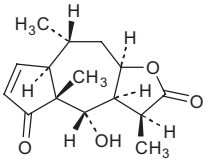
Major chemical constituents

The major constituents include the essential oil (0.5%), fatty acids (content not specified), thymol (content not specified), pseudoguaianolide sesquiterpene lactones (0.2–0.8%) and flavonoid glycosides (0.2–0.6%) (*4, 9, 14*). The primary sesquiterpene lactones are helenalin, 11α,13-dihydrohelenalin and their fatty acid esters. Flavonoids include glycosides and/or glucuronides of spinacetin, hispidulin, patuletin and isorhamnetin, among others (*4, 7, 9, 14–16*). The structures of helenalin and 11α,13-dihydrohelenalin are presented below.

helenalin



11α,13-dihydrohelenalin



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As a topical counterirritant for treatment of pain and inflammation resulting from minor injuries and accidents, including bruises, ecchymoses,

haematomas and petechiae (*1, 17*). Treatment of inflammation of the oral mucous membranes, insect bites and superficial phlebitis (*17*).

Uses described in traditional medicine

Treatment of indigestion, cardiovascular disease, and rheumatism. As an emmenagogue (*9*).

Pharmacology

Experimental pharmacology

Analgesic and anti-inflammatory activity

In vitro, helenalin, 5.0 µmol/l, significantly ($P < 0.01$) suppressed the activity of prostaglandin synthetase in mouse and rat homogenates, and human polymorphonuclear neutrophils, indicating an anti-inflammatory effect (*18*). Human polymorphonuclear neutrophil chemotaxis was inhibited by helenalin, 5.0 µmol/l, in vitro. It was concluded that the α-methylene-γ-lactone moiety played a role in the anti-inflammatory activity of this compound (*18*). Helenalin, 4.0 µmol/l, selectively inhibited the transcription factor nuclear factor (NF)-κβ (*19*).

Intragastric administration of 100.0 mg/kg body weight (bw) of an 80% ethanol extract of Flos Arnicae reduced carrageenan-induced hind paw oedema by up to 29% in rats (*20*). Intraperitoneal administration of 2.5–5.0 mg/kg bw of helenalin significantly ($P < 0.001$) inhibited carrageenan-induced hind paw oedema in rats by 77% after 72 hours (*21*). Intraperitoneal administration of 20.0 mg/kg bw of helenalin strongly inhibited acetic acid-induced writhing by 93% in mice but did not have analgesic effects in mice in the hot-plate test. Intraperitoneal administration of 2.5 mg/kg bw of helenalin to rats inhibited arthritis induced by *Mycobacterium butyricum* by 87% (*21*).

Antioxidant activity

The effect of a tincture of Flos Arnicae on lipid peroxidation and glutathione metabolism in rat liver was assessed following induction of hepatitis by the administration of carbon tetrachloride. Intragastric administration of 0.2 ml/g bw of the tincture to rats decreased the rate of lipid oxidation and increased the activities of the enzymes involved in glutathione metabolism (*22*). Intragastric administration of 0.2 ml/g bw of the tincture per day for 14 days to rats with hepatitis induced by carbon tetrachloride led to a normalization of the hydrolytic enzymes (*23*).

Antitumour activity

Helenalin is cytotoxic to a wide variety of cancer cell lines in vitro, with a median effective dose (ED_{50}) range of 0.03–1.0 µg/ml (*24–27*). Intraperi-

toneal administration of 1.5–33.3 mg/kg bw of helenalin to mice and rats had antitumour activity against a variety of chemically induced tumours (*28–30*).

Cardiovascular effects

Flos Arnicae and extracts of the flower heads have cardiotonic and hypotensive effects in various animal models. Intravenous administration of a single dose of 1.0 ml of a tincture of the flower heads to rabbits had negative chronotropic effects and reduced blood pressure (*31*). Intravenous administration of 1.0 ml of an aqueous or 95% ethanol extract of the flower heads had cardiotonic effects in frogs, and a tincture demonstrated hypotensive activity in rabbits after intravenous administration of 1.0 ml (*32, 33*). A 30% ethanol extract of the flower heads, 0.1–0.3% in the bath medium, had positive inotropic effects in isolated guinea-pig hearts (*33*). Intravenous administration of 5.0 g/kg bw of a fluid extract or tincture of the flower heads increased the blood pressure of cats and guinea-pigs (*34*).

Helenalin, 50.0 µg/ml, decreased intracellular calcium levels in cultured fibroblasts, and potentiated the responses induced by vasopressin and bradykinin (*35*). Intravenous administration of helenalin had cardiotoxic effects in mice (25.0 mg/kg bw) and dogs (90.0 mg/kg bw) (*36*).

Choleretic activity

Intravenous administration of 1.0 ml of a 95% ethanol extract of the flower heads to dogs increased bile secretion by 25–120% (*37*). Intragastric administration of a hot aqueous extract of the flower heads had choleretic effects in rats (dose not specified) (*38*) and dogs (50.0 ml/animal) (*39*).

Toxicology

The oral median lethal dose (LD_{50}) of a 30% ethanol extract of the flower heads was 37.0 ml/kg in mice (*33*). The intragastric LD_{50} for helenalin has been established for numerous species: mice 150.0 mg/kg bw, rats 125.0 mg/kg bw, rabbits 90.0 mg/kg bw, hamsters 85.0 mg/kg bw and ewes 125.0 mg/kg bw (*40*).

Uterine stimulant effects

Intragastric administration of a tincture of the flower heads (dose not specified) had uterine stimulant effects in guinea-pigs (*41*). Intragastric administration of a hot aqueous extract of the flower heads (dose not specified) stimulated uterine contractions in rats (*38*).

Clinical pharmacology

No information available. Clinical trials of homeopathic preparations were not assessed.

Adverse reactions

Numerous cases of dermatitis of toxic or allergic origin have been reported (*42*), usually following prolonged, external application of a tincture of Flos Arnicae. The compounds responsible for the hypersensitivity reaction are the sesquiterpene lactones helenalin and helenalin acetate (*43*). Cross-reactivity to other Asteraceae flowers has been reported (*44–47*).

The flower heads are irritant to the mucous membranes and ingestion may result in gastroenteritis, muscle paralysis (voluntary and cardiac), an increase or decrease in pulse rate, heart palpitations, shortness of breath and death. A fatal case of poisoning following the ingestion of 70.0 g of a tincture of the flower heads has been reported (*48*).

A case of severe mucosal injuries following the misuse of an undiluted mouth rinse with a 70% alcohol content, which also contained oil of peppermint and Flos Arnicae, has been reported (*49*).

Contraindications

Flos Arnicae is used in traditional systems of medicine as an emmenagogue (*9*), and its safety during pregnancy and nursing has not been established. Therefore, in accordance with standard medical practice, the flower heads should not be administered to pregnant or nursing women. Flos Arnicae is also contraindicated in cases of known allergy to *Arnica* or other members of the Asteraceae (Compositae) (*37, 42, 50, 51*).

Warnings

A fatal case of poisoning following the ingestion of 70.0 g of a tincture of Flos Arnicae has been reported (*48*). Internal use of Flos Arnicae or extracts of the flower heads is not recommended. For external use only. Do not apply to open or broken skin. Keep out of the reach of children (*17*).

Precautions

General

Avoid excessive use. Chronic, frequent external applications may induce allergy-related skin rashes with itching, blister formation, ulcers and superficial necrosis. Prolonged treatment of damaged or injured skin or indolent leg ulcers may induce the formation of oedematous dermatitis with the formation of pustules (*17*).

Carcinogenesis, mutagenesis, impairment of fertility

Helenalin has cytotoxic effects in vitro (see Experimental pharmacology). However, in the *Salmonella*/microsome assay, helenalin was not muta-

genic in *S. typhimurium strains* TA102, TA98 or TA100 at concentrations of up to 30 µg/ml (*52, 53*).

Pregnancy: teratogenic effects
Intraperitoneal administration of 6.0–20.0 mg/kg bw of helenalin was not teratogenic in mice (*21*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Warnings. For external use only. Do not apply to abraded or broken skin.

Other precautions
No information available on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Dried flower heads and other galenical preparations. Store protected from light and moisture (*7*).

Posology
(Unless otherwise indicated)
For external applications only, apply undiluted externally on the affected area two or three times daily: infusion for compresses, 2 g of Flos Arnicae per 100 ml water; tincture for compresses, one part Flos Arnicae to 10 parts 70% ethanol; mouth rinse, 10-fold dilution of tincture, do not swallow; ointment, 20–25% tincture of Flos Arnicae or not more than 15% essential oil (vehicle not specified) (*17*).

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Folium Azadirachti

Definition

Folium Azadirachti consists of the dried leaves of *Azadirachta indica* A. Juss. (Meliaceae) (*1–4*).

Synonyms

Melia azadirachta L., *M. indica* (A. Juss.) Brand., *M. indica* Brand. (*1–3*).

Selected vernacular names

Abodua, aforo-oyinbo, anwe egyane, arista, azad dirakht, azadarakht, azedarach, bead tree, bevinama, bevu, bewina mara, bodetso, bo-nim, cape lilac, chajara hourra, chichaâne arbi, China berry, China tree, cót anh, darbejiya, dogo yaro, dogo'n yaro, dogonyaro, dogoyaro, dongo yaro, dua gyane, gori, gringging, holy tree, igi-oba, imba, Indian lilac, Indian lilac tree, Indian neem tree, Indian sadao, Intaran, isa-bevu, jaroud, kahibevu, kingtsho, kiswahhili, kohhomba, kohumba, koummar, kuman masar, kuman nasara, kwinin, labkh, lilac de perse, lilas des indes, liliti, limb, limba, limbado, limado, linigbe, mahanim, mahanimba, mahnimu, mak tong, margosa, margosa tree, margose, marrar, mimba, mindi, miro tahiti, mwarobaini, neeb, neem, neem sikha, nim, nim tree, nimba, nimbatikta, nimgach, nivaquine, ogwu akom, oilevevu, ouchi, Persian lilac, phãk kã dão, picumarda, sa-dao, sa-dao baan, sadao India, sdau, salien, sandan, sandannoki, sãu dâu, senjed talhk, shajarat el horrah, shereesh, tâak, tâakhak, touchenboku, vembu, vemmu, vepa, veppam, veppu, white cedar, xoan dào, zanzalakht, zaytoon (*1–9*).

Geographical distribution

Indigenous to India, and widely distributed in South and South-East Asia. Cultivated in Africa, the South Pacific Islands, South and Central America and Australia, and in southern Florida and California, United States of America (*1–3*, *8–11*).

Description

A straight-boled deciduous tree 6–25 m high. Bark dark-brown, externally fissured, with a buff inner surface, fibrous fracture. Leaves alternately arranged, pinnately compound, up to 40 cm long, composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Inflorescences axillary panicles; flowers numerous, white, pedicillate, about 1.0 cm wide. Fruits yellowish drupes, oblong, about 1.5 cm long, containing thin pulp surrounding a single seed. When bruised, leaves and twigs emit an onion-like odour (*1–3, 8, 11*).

Plant material of interest: dried leaves

Other plant parts used, but not included in this monograph: flowers, seeds, stem bark, oil (*1–3, 8, 10, 12*).

General appearance

Compound leaves up to 40 cm long composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Glabrous dark green upper surface, paler underside (*1–3*).

Organoleptic properties

Odour: characteristic, alliaceous; taste: bitter (*1–3*).

Microscopic characteristics

Lower epidermis with anomocytic stomata and occasional unicellular trichomes. Two layers of palisade cells are found below the upper epidermis. Spongy parenchyma exhibits intercellular spaces and secretory cells, which are abundant on the borderline with the palisade cells. Anticlinal cell walls are almost straight. Mesophyll contains rosette crystals. Collenchyma interrupts mesophyll on both upper and lower surfaces in the midrib region. Vascular bundles strongly curved, lignified, collateral (*1–3*).

Powdered plant material

Green and characterized by the presence of cortical cells of the rachis, fragments of palisade cells, hairs, fibres, wood fibres, spiral lignified vascular elements, epidermal tissues of the leaf with characteristic anomocytic stomata and large pit cells with intercellular spaces. Epidermal cell walls straight (*2, 3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), microchemical tests (*2*) and thin-layer chromatography (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2% (*4*).

Total ash

Not more than 10% (*4*).

Acid-insoluble ash

Not more than 1% (*4*).

Water-soluble extractive

Not less than 19% (*4*).

Alcohol-soluble extractive

Not less than 13% (*4*).

Loss on drying

Not more than 3% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

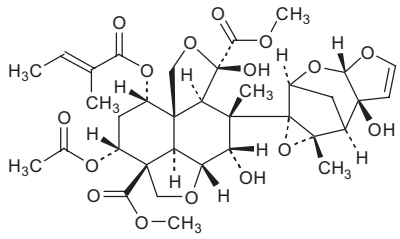
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

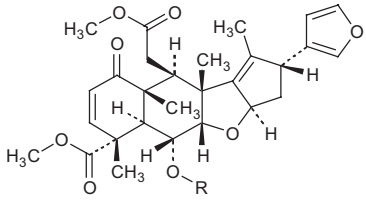
High-performance liquid chromatography methods are available for the quantitative determination of oxidized tetranortriterpenes (*16, 17*).

Major chemical constituents

The major characteristic constituents are oxidized tetranortriterpenes including azadirachtin (azadirachtin A), 3-tigloylazadirachtol (azadirachtin B), 1-tigloyl-3-acetyl-11-hydroxy-meliacarpin (azadirachtin D), 11-demethoxycarbonyl azadirachtin (azadirachtin H), 1-tigloyl-3-acetyl-11-hydroxy-11-demethoxycarbonyl meliacarpin (azadirachtin I), azadiriadione, azadirachtanin, epoxyazadiradione, nimbin, deacetylnimbin, salannin, azadirachtolide, isoazadirolide, margosinolide, nimbandiol, nimbinene, nimbolin A, nimbocinone, nimbocinolide, nimbolide, nimocin, nimocinol and related derivatives (*9, 11, 18–20*). The structures of azadirachtin, nimbin and deacetylnimbin are presented below.



azadirachtin



nimbin R = CO-CH_3

deacetylnimbin R = H

Medicinal uses

Uses supported by clinical data

External applications for treatment of ringworm (*21*). However, data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Treatment of worm and lice infections, jaundice, external ulcers, cardiovascular disease, diabetes, gingivitis, malaria, rheumatism and skin disorders. External applications for treatment of septic wounds and boils (*6, 8*).

Uses described in traditional medicine

Treatment of allergic skin reactions, asthma, bruises, colic, conjunctivitis, dysentery, dysmenorrhoea, delirium in fever, gout, headache, itching due to varicella, jaundice, kidney stones, leprosy, leukorrhoea, psoriasis, scabies, smallpox, sprains and muscular pain, syphilis, yellow fever, warts and wounds (*10, 22*). Also used as an antivenin, contraceptive, emmenagogue, tonic, stomatic and vermicide (*9*).

Pharmacology

Experimental pharmacology

Anxiolytic and analgesic activities

Intragastric administration of 10.0–200.0 mg/kg body weight (bw) of an aqueous extract of Folium Azadirachti produced anxiolytic effects similar to those of 1.0 mg/kg bw of diazepam in rats in the elevated-plus-maze and open-field behaviour tests (*23*).

The analgesic effect of an extract of the leaves was assessed in mice using the acetic acid writhing test and the tail flick test. Intragastric administration of 10.0–100.0 mg/kg bw of the extract reduced the incidence of writhing and enhanced tail-withdrawal latencies (*24*).

Antiandrogenic activity

Intragastric administration of 20.0 mg, 40.0 mg or 60.0 mg of powdered leaves per day to rats for 24 days resulted in a decrease in the weight of the seminal vesicles and ventral prostate, and a reduction in epithelial height, nuclear diameter and secretory material in the lumen of these organs. Decreases in total protein and acid phosphatase activities were also observed. These regressive histological and biochemical changes suggest that the leaves have an antiandrogenic property (*25*). Histological and biochemical changes were also observed in the caput and cauda epididymis of rats treated orally with similar doses of the powdered leaves given daily for 24 days. The height of the epithelium and the diameter of the nucleus in both regions were reduced. Serum testosterone concentrations were also reduced in animals receiving the highest dose (*26*). Intragastric administration of an aqueous extract of the leaves (dose not specified) to male mice daily for 10 weeks resulted in a significant ($P < 0.01$) reduction in total serum testosterone and bilirubin (*27*).

Antihepatotoxic activity

The effect of an aqueous extract of the leaves was evaluated in paracetamol-induced hepatotoxicity in rats. Intragastric administration of 500.0 mg/kg bw of the extract significantly ($P < 0.01$) reduced elevated levels of serum

aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase (*28*).

Anti-inflammatory activity

Intragastric administration of 200.0 mg/kg bw of an aqueous extract of the leaves to rats decreased inflammation and swelling in the cotton pellet granuloma assay (*29*). Intraperitoneal injection of 200.0–400.0 mg/kg bw of an aqueous extract of the leaves to rats reduced carrageenan-induced footpad oedema (*30*).

Antihyperglycaemic activity

A hypoglycaemic effect was observed in normal and alloxan-induced diabetic rabbits after administration of 50.0 mg/kg bw of an ethanol extract of the leaves. The effect was more pronounced in diabetic animals, and reduced blood glucose levels. The hypoglycaemic effect was comparable to that of glibenclamide. Pretreatment with the extract 2 weeks prior to alloxan treatment partially prevented the rise in blood glucose levels as compared with control diabetic animals (*31*). Intragastric administration of 50.0–400.0 mg/kg bw of a 70% ethanol extract of the leaves significantly ($P < 0.001$) reduced elevated blood glucose levels in normal and streptozocin-induced diabetic rats (*32–34*). A 70% ethanol extract of the leaves significantly ($P < 0.05$) blocked the inhibitory effect of serotonin on insulin secretion mediated by glucose in isolated rat pancreas (*35*).

Antimalarial activity

An aqueous or ethanol extract of the leaves inhibited the growth of *Plasmodium falciparum* in vitro, with median inhibitory concentrations of 115.0 µg/ml and 5.0 µg/ml, respectively. Nimbolide, a constituent of the extract, inhibited the growth of *P. falciparum* in vitro with a median effective concentration of 2.0 µg/ml (*36*). However, intragastric administration of 746.0 mg/kg bw of the aqueous extract, 62.5 mg/kg bw of the ethanol extract or 12.5 mg/kg bw of nimbolide had no such effect in *Plasmodium*-infected mice (*36*). *P. berghei*-infected mice showed parasite suppression after intragastric administration of 125.0–500.0 mg/kg bw of a dried methanol extract of the leaves per day for 4 days, but all the animals died after 5 days (*37*). A 95% ethanol extract of the leaves at concentrations of up to 500.0 mg/ml did not inhibit the growth of *P. falciparum* in vitro (*38*).

Antimicrobial and antiviral activity

A methanol extract of the leaves, 1.0 mg/ml, inhibited plaque formation in six antigenic types of coxsackievirus B at 96 hours in vitro. The minimal inhibitory concentrations were not toxic to Vero African green mon-

key kidney cells. The subtoxic concentration was 8.0 mg/ml and the cytotoxic concentration was 10.0 mg/ml (*39*).

An aqueous extract of the leaves, at various concentrations depending on the organism, inhibited the growth of *Bacteroides gingivalis*, *B. intermedius, Streptococcus salivarius* and *S. viridans* in vitro (*40*). A petroleum ether extract of the leaves, at various concentrations depending on the organism, inhibited the growth of *Epidermophyton floccosum, Microsporum canis, M. gypseum, Trichophyton concentricum, T. violaceum* and *T. rubrum* (*41*).

Antioxidant activity

The effect of the leaves on hepatic lipid peroxidation and antioxidant status during gastric carcinogenesis induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine was assessed in rats. Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves decreased lipid peroxidation in the liver of tumour-bearing animals, which was accompanied by a decrease in the activities of glutathione peroxidase, glutathione-*S*-transferase and γ-glutamyl transpeptidase, and a reduction in glutathione level. Administration of 100.0 mg/kg bw of an extract of the leaves suppressed lipid peroxidation and increased hepatic levels of glutathione and glutathione-dependent enzymes (*42*). Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves three times per week to hamsters with buccal pouch carcinogenesis induced by 7,12-dimethylbenz[α]anthracene reduced lipid peroxidation and increased the glutathione concentration in the oral mucosa of tumour-bearing animals (*43*).

Antiulcer activity

The antiulcer effects of an aqueous extract of the leaves were investigated in rats exposed to 2-hour cold-restraint stress or given ethanol for 1 hour. The extract, administered orally in doses of 10.0 mg/kg bw, 40.0 mg/kg bw or 160.0 mg/kg bw as single- or five-dose pretreatments produced a dose-dependent reduction in the severity of gastric ulcers induced by stress and a decrease in gastric mucosal damage provoked by ethanol. The extract prevented mast cell degranulation and increased the amount of adherent gastric mucus in stressed animals (*44*). Intragastric administration of 40.0 mg/kg bw of an aqueous extract of the leaves per day for 5 days to rats inhibited stress-induced depletion of gastric wall adherent cells and mucus production (*44*).

Cardiovascular effects

Intragastric administration of 200.0 mg/kg bw of an alcohol extract of the leaves to anaesthetized rabbits decreased the heart rate from 280 to

150 beats per minute, and had a weak antiarrhythmic effect against ouabain-induced dysrhythmia (*45*). Intravenous administration of 100.0 mg/kg bw, 300.0 mg/kg bw or 1000.0 mg/kg bw of an ethanol extract of the leaves to rats resulted in initial bradycardia followed by cardiac arrhythmias. The treatment produced a dose-related fall in blood pressure that was immediate, sharp and persistent. Pretreatment with atropine or mepyramine failed to prevent the hypotensive effect of the extract (*46*).

Immune effects

The effect of an aqueous extract of the leaves on humoral and cell-mediated immune responses was assessed in mice treated with ovalbumin. At doses of 10.0 mg/kg bw, 30.0 mg/kg bw or 100.0 mg/kg bw, the extract produced no appreciable effects on organ/body weight indices for liver, spleen and thymus compared with controls. In tests for humoral immune responses, IgM and IgG levels, and antiovalbumin antibody titres were higher in mice receiving the highest dose of extract than in animals in the control group. In tests for cell-mediated immune responses, mice receiving the highest dose of extract showed enhancement of macrophage migration inhibition and footpad thickness (*47*). Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves to normal and stressed rats lowered blood glucose and triglyceride levels, attenuated stress-induced elevations of cholesterol and urea, and suppressed humoral responses (*48*).

The effect of powdered leaves on humoral and cell-mediated immune responses was assessed in chickens infected with infectious bursal disease. A dose of 2.0 g/kg bw per day given in the diet increased antibody titres against Newcastle disease virus antigen and enhanced inflammatory reactions to chloro-2,4-dinitrobenzene in the skin contact test (*49*).

Toxicology

Chickens fed diets containing the powdered leaves, 2% or 5%, from the 7th to the 35th day of age, and then a control diet for 2 weeks, showed a reduction in body weight gain and efficiency of feed use compared with controls. The main pathological changes observed included an increase in lactic dehydrogenase, glutamic-oxaloacetic transaminase and alkaline phosphatase activities, an increase in uric acid and bilirubin concentrations, and a decrease in total serum protein levels. There were marked reductions in the values of erythrocyte count, haemoglobin concentration, packed cell volume, mean corpuscular volume and mean corpuscular haemoglobin, which were associated with yellow discoloration on the legs and hepatonephropathy (*50*).

Intragastric administration of 50.0 mg/kg bw or 200.0 mg/kg bw of aqueous suspensions of the leaves per day to goats and guinea-pigs over a period of up to 8 weeks produced a progressive decrease in body weight, weakness, inappetence, loss of condition and decreases in the pulse and respiratory rates. In goats, the higher dose produced tremors and ataxia during the last few days of treatment. No statistically significant haematological changes were observed, although there was a tendency towards lowered erythrocyte counts, packed cell volume and haemoglobin levels. The treatment increased aspartate transferase and sorbitol dehydrogenase activities, and concentrations of cholesterol, urea, creatinine and potassium in the plasma. No significant changes in the plasma concentrations of sodium, chloride or bilirubin were detected. Autopsy of treated goats revealed areas of haemorrhagic erosion. The hearts appeared flappy and in some animals there was hydropericardium. Histopathologically, there was evidence of various degrees of haemorrhage, congestion, and degeneration in the liver, kidney, lung, duodenum, brain and seminiferous tubules (*51*).

The effect of intragastric administration of 40.0 mg/kg bw and 100.0 mg/kg bw of an aqueous extract of the leaves per day for 20 days on thyroid function was assessed in male mice. The higher dose decreased serum tri-iodothyronine and increased serum thyroxine concentrations. There was a concomitant increase in hepatic lipid peroxidation and a decrease in glucose-6-phosphatase activity. The lower dose produced no significant changes (*52*).

The median lethal dose of a 50% ethanol extract of the leaves in mice was 681.0 mg/kg bw when administered by intraperitoneal injection (*53*).

Clinical pharmacology

A 70% ethanol extract of the leaves was used for the treatment of ringworm in seven patients. External applications of a 40% solution of the extract twice per day to the affected areas for 5–10 days were reported to be effective (no further details available) (*21*).

Adverse reactions

A case of ventricular fibrillation and cardiac arrest due to neem leaf poisoning has been reported (*54–56*). Contact dermatitis has also been reported (*57*).

Contraindications

Owing to potential genotoxic effects (*58*), the leaves should not be administered during pregnancy or nursing, or to children under the age of 12 years.

Warnings

No information available.

Precautions

Drug interactions

Administration of Folium Azadirachti may reduce blood glucose levels and should therefore be used with caution in insulin-dependent diabetic patients or patients taking oral antihyperglycaemic drugs.

Carcinogenesis, mutagenesis, impairment of fertility

A petroleum ether extract of the leaves was not mutagenic in the *Salmonella*/microsome assay at concentrations of 0.1 ml/plate using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 (*59*).

Intragastric administration of 5.0 mg/10 g bw, 10.0 mg/10 g bw or 20.0 mg/10 g bw of an ethanol extract of the leaves per day for 7 days to mice significantly ($P < 0.05$) increased the incidence of structural and mitotic disruptive changes in metaphase chromosomes of bone marrow cells on days 8, 15 and 35 (*58*). Intragastric administration of 100.0 mg/kg bw of an ethanol extract of the leaves per day for 21 days had no effect on spermatogenesis in male rats, and no effect on implantation in female animals mated with treated males (*60*).

Pregnancy: teratogenic effects

Intragastric administration of 200.0 mg/kg bw of an acetone or 50% ethanol extract of the leaves to pregnant rats on days 1–7 of pregnancy did not produce any teratogenic or embryotoxic effects (*61*).

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test reactions; or non-teratogenic effects in pregnancy.

Dosage forms

Dried leaves for infusions and decoctions, and extracts and tinctures (*8*). Store leaves in a cool, dry place (*3*).

Posology

(Unless otherwise indicated)
Infusion (1:20): 15–30 ml. Tincture (1:5): 4–8 ml (*8*). External applications: 70% ethanol extract of the leaves diluted to 40%, apply twice daily (*21*).

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Oleum Azadirachti

Definition
Oleum Azadirachti consists of the fixed oil obtained from dried seeds of *Azadirachta indica* A. Juss. (Meliaceae).

Synonyms
Melia azadirachta L., *M. indica* (A. Juss.) Brand., *M. indica* Brand. (*1–3*).

Selected vernacular names
Abodua, aforo-oyinbo, anwe egyane, arista, azad dirakht, azadarakht, azedarach, bead tree, bevinama, bevu, bewina mara, bodetso, bo-nim, cape lilac, chajara hourra, chichaâne arbi, China berry, China tree, cót anh, darbejiya, dogo yaro, dogo'n yaro, dogonyaro, dogoyaro, dongo yaro, dua gyane, gori, gringging, holy tree, igi-oba, imba, Indian lilac, Indian lilac tree, Indian neem tree, Indian sadao, Intaran, isa-bevu, jaroud, kahibevu, kingtsho, kiswahhili, kohhomba, kohumba, koummar, kuman masar, kuman nasara, kwinin, labkh, lilac de perse, lilas des indes, liliti, limb, limba, limbado, limado, linigbe, mahanim, mahanimba, mahnimu, mak tong, margosa, margosa tree, margose, marrar, mimba, mindi, miro tahiti, mwarobaini, neeb, neem, neem sikha, nim, nim tree, nimba, nimbatikta, nimgach, nivaquine, ogwu akom, oilevevu, ouchi, Persian lilac, phãk kã dão, picumarda, sa-dao, sa-dao baan, sadao India, sdau, salien, sandan, sandannoki, sãu dâu, senjed talhk, shajarat el horrah, shereesh, tâak, tâakhak, touchenboku, vembu, vemmu, vepa, veppam, veppu, white cedar, xoan dào, zanzalakht, zaytoon (*1–9*).

Geographical distribution
Indigenous to India, and widely distributed in South and South-East Asia. Cultivated in Africa, the South Pacific Islands, South and Central America and Australia, and in southern Florida and California, United States of America (*1–3, 7, 10, 11*).

Description
A straight-boled deciduous tree 6–25 m high. Bark dark-brown, externally fissured, with a buff inner surface, fibrous fracture. Leaves alter-

nately arranged, pinnately compound, up to 40 cm long, composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Inflorescences axillary panicles; flowers numerous, white, pedicillate, about 1.0 cm wide. Fruits yellowish drupes, oblong, about 1.5 cm long, containing thin pulp surrounding a single seed. When bruised, leaves and twigs emit an onion-like odour (*1–3, 7, 11*).

Plant material of interest: fixed oil

General appearance

No information available.

Organoleptic properties

Odour: characteristic alliaceous (*10*); taste: no information available.

General identity tests

Macroscopic examination and thin-layer chromatography (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Chemical

Relative density 0.913–0.919 (*13*); refractive index 1.462–1.466 (*13*); saponification value 196.0 (*13*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

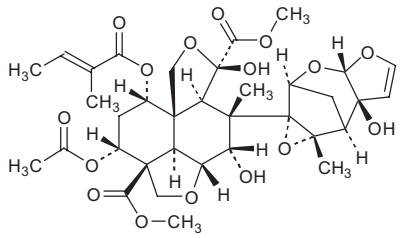
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Chemical assays

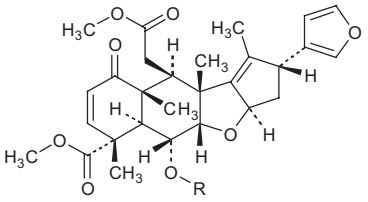
A high-performance liquid chromatography procedure is available for the quantitative determination of oxidized tetranortriterpenes (*16*).

Major chemical constituents

The major constituents are oxidized tetranortriterpenes including azadirachtin (azadirachtin A), azadiriadione, epoxyazadiradione, azadirone, nimbidin, nimbin, deacetylnimbin, salannin, gedunin, mahmoodin, 17-hydroxydiradione and related derivatives (*9, 11, 17–19*). The structures of azadirachtin, nimbin and deacetylnimbin are presented below:



azadirachtin



nimbin R = CO-CH_3

deacetylnimbin R = H

Medicinal uses

Uses supported by clinical data

As a contraceptive for intravaginal use (*20*), as a mosquito repellent (*21*), and for treatment of vaginal infections (*22*). However, further controlled clinical trials are needed before the oil can be recommended for general use.

Uses described in pharmacopoeias and well established documents

Treatment of gastric ulcers, cardiovascular disease, malaria, rheumatism and skin disorders. External applications for treatment of septic wounds, ulcers and boils (*7*).

Uses described in traditional medicine

Treatment of allergic skin reactions, asthma, bruises, colic, conjunctivitis, dysmenorrhoea, fever, gout, headache, itching due to varicella, kidney stones, leukorrhoea, psoriasis, scabies, sprains and muscular pain, and wounds (*10, 11*). As an emmenagogue, tonic, stomatic and vermicide (*9*).

Pharmacology

Experimental pharmacology

Antifertility activity

Oleum Azadirachti, 0.6 ml, was given to female rats by intragastric administration on days 8–10 of pregnancy, after confirming the presence

and number of embryo implants surgically on day 7. The animals were examined again under anaesthesia on day 15 of pregnancy to check the number of developing embryos. Controls received an equivalent regime of peanut oil. Complete resorption of embryos was observed on day 15 of pregnancy in every animal treated with Oleum Azadirachti while embryos were developing normally in controls (*23*). Intragastric administration of 6.0 ml of the oil per day for 60 days to female baboons induced abortion in pregnant animals (*24*).

A single intrauterine application of 100.0 µl of the oil produced a reversible block in fertility lasting for 107–180 days in female rats (*25*) and 7–11 months in monkeys (*26*). In an attempt to find an alternative to vasectomy for long-term male contraception, the effect of a single intra-vas application of the oil was assessed in male rats. Animals with proven fertility were given a single dose of 50.0 µl of the oil in the lumen of the vas deferens on each side. Control animals received the same volume of peanut oil. Animals were allowed free access to mating for 4 weeks after the treatment, with females of proven fertility. While the control animals impregnated their female partners, all males treated with Oleum Azadirachti remained infertile throughout the 8-month observation period. Epididymal and vas histologies were normal, with no inflammatory changes or obstruction. Intra-vas administration of the oil resulted in a block of spermatogenesis without affecting testosterone production. The seminiferous tubules, although reduced in diameter, appeared normal and contained mostly early spermatogenic cells. No anti-sperm antibodies were detected in the serum (*27*).

Subcutaneous administration of up to 0.3 ml of the oil to rats had no estrogenic, anti-estrogenic or progestational activity, and appeared not to interfere with the action of progesterone (*28*). Intravaginal application of 2.50 µl–0.25 ml of the oil to pregnant rats induced abortion (*29*).

The oil, 10–25%, inhibited fertilization in isolated mouse ova as assessed by sperm–egg interaction, and impaired the development of fertilized ova in vitro (*30*). In other investigations, the active constituents of the oil were identified to be a mixture of six compounds comprising saturated, mono and di-unsaturated free fatty acids and their methyl esters (*31*). The oil, 0.25–25.00 mg/ml, had spermicidal effects on human and rat sperm in vitro (*32, 33*).

Antihyperglycaemic activity

Intragastric administration of 21.0 mg/kg body weight (bw) of the oil reduced blood glucose levels in rats (*34*). A significant ($P < 0.01$) reduction in blood glucose levels was observed in normal and alloxan-induced dia-

betic rabbits after administration of 200.0 mg of the oil; the effect was more pronounced in diabetic animals (*35*).

Anti-inflammatory activity

The anti-inflammatory effects of nimbidin were assessed and compared with phenylbutazone. Intramuscular administration of 40.0 mg/kg bw of nimbidin reduced acute paw oedema in rats induced by carrageenan and kaolin. Formalin-induced arthritis in ankle joints and fluid exudation due to granuloma induced by croton oil in rats were also suppressed by similar treatment with the compound. In the acute phase of inflammation, nimbidin at 40.0 mg/kg bw was more active than phenylbutazone at 100.0 mg/kg bw (*36*). Intramuscular administration of 50.0 mg/kg bw of the oil reduced granuloma induced by cotton pellet in rats (*37*).

Antimicrobial and antiviral activity

The efficacy of a petroleum ether extract of the oil was investigated for its antimicrobial activity against certain bacteria and fungi and poliovirus, as compared with the oil. The extract had stronger antimicrobial activity than the oil and, in vitro at 2.0 mg/ml, inhibited the growth of *Escherichia coli* and *Klebsiella pneumoniae*, which were not inhibited by the oil. The extract was active against *Candida albicans* (minimum inhibitory concentration 0.25 mg/ml) and had antiviral activity against poliovirus replication in Vero African green monkey kidney cell lines at 50.0 µg/ml (*38*).

Intravenous administration of 60.0 mg/kg bw of the oil twice per day for 7 days protected mice from systemic candidiasis, as shown by enhanced survival and a reduction in colony-forming units of *C. albicans* in various tissues (*38*).

The oil inhibited the growth of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *S. pyogenes* in vitro at a concentration of 1.5–6.0% (*39*). A petroleum ether extract of the oil inhibited the growth of *Epidermophyton floccosum, Microsporum canis, M. gypseum, Trichophyton concentricum, T. rubrum* and *T. violaceum* (*40*).

Antiulcer activity

Intragastric administration of 40.0 mg/kg bw of nimbidin showed antiulcer activity in various experimental models (gastric lesions induced by acetylsalicylate, stress, serotonin and indometacin) in rats. The compound also protected against cysteamine- and histamine-induced duodenal lesions in rodents (*41*).

Estrogenic activity
Subcutaneous administration of 0.2–6.0 ml/kg bw of the oil to normal or ovariectomized rats had no estrogenic effects: there was no increase in uterine wet weight or disruption of the estrous cycle (*28, 29*).

Immune effects
Mice received Oleum Azadirachti, 150.0 µl/animal, or an emulsifying agent, with or without peanut oil, by intraperitoneal injection. Peritoneal lavage on subsequent days showed an increase in the number of leukocytic cells on day 3 following treatment with Oleum Azadirachti, and peritoneal macrophages exhibited enhanced phagocytic activity and expression of major histocompatability complex class II antigens. Treatment also induced the production of γ-interferon. The spleen cells of oil-treated animals showed a significantly higher lymphocyte proliferative response to in vitro challenge with concanavalin A or tetanus toxin than those of controls. Pretreatment with the oil did not augment the anti-tetanus-toxin antibody response. The results of this study indicate that the oil acts as a nonspecific immunostimulant and that it selectively activates cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge (*42*). Intraperitoneal administration of the oil to mice (150.0 µl/animal) and rats (120.0 µl/animal) enhanced phagocytosis of macrophages (*42, 43*).

Toxicology
Studies of the oral acute toxicity of the oil in rats and rabbits showed dose-related pharmacotoxic symptoms along with a number of biochemical and histopathological indices of toxicity. The 24-hour oral median lethal dose was 14.0 ml/kg bw in rats and 24.0 ml/kg bw in rabbits. Prior to death, all animals exhibited pharmacotoxic symptoms of a similar type and severity; the lungs and central nervous system were the target organs (*44*).

Intragastric administration of the oil to mice was not toxic at a dose of 2.0 ml. The oil (dose not specified) was nonirritant when applied to the skin of rabbits in a primary dermal irritation test. In a subacute dermal toxicity study, rabbits exposed to the oil (dose not specified) daily for 21 days showed no significant changes in body weight or organ:body weight ratio, serum oxaloacetic transaminase and pyruvic transaminase levels, and blood glucose and urea nitrogen values. No treatment-related histopathological changes were observed (*45*).

In a three-generation study carried out according to a World Health Organization/United States Food and Drug Administration protocol, groups of 15 male and 15 female rats were fed a diet containing 10% Oleum Azadirachti or peanut oil. Reproductive toxicology was monitored

for three generations. There were no adverse effects on the reproductive parameters in either group (*46*).

A group of 10 pregnant rats received 2.0 ml/kg bw of the oil by gastric administration daily and the animals were allowed to deliver at term. Six of the treated animals died between days 6 and 13 of pregnancy. Among the four remaining animals that delivered, one delivered a seemingly normal pup on day 27, but the pup died after 4 days. Autopsy performed on day 16 of pregnancy suggested that fetal resorption had occurred; however, no indication was given as to whether fetuses were normal (*47*).

Clinical pharmacology

Contraceptive activity

In an uncontrolled clinical trial involving 225 healthy fertile women aged 18–35 years performed to assess the efficacy of the oil as an antifertility agent, subjects were instructed to insert 1 ml of the oil into the vagina with a plastic applicator 5 minutes prior to coitus. No other contraception was used. After 16 months of use only three pregnancies due to drug failure were reported; there were 30 pregnancies due to noncompliance (i.e. in women who did not use the oil as instructed) (*20*).

Antibacterial activity

In a 2-week double-blind, placebo-controlled clinical trial involving 55 women with abnormal vaginal discharge due to bacterial vaginosis, subjects were instructed to insert 5.0 ml of the oil or placebo oil into the vagina daily. Treatment with the test oil was reported to cure the symptoms of the infection (*22*).

Insect repellent activity

In a field study carried out to evaluate the mosquito repellent action of the oil in villages in a forested area in Mandla District, Madhya Pradesh, India, various concentrations of the oil were mixed with coconut oil (1–4%) and applied to the exposed body parts of human volunteers. The mixture provided 81–91% protection from the bites of anopheline mosquitoes during a 12-hour period of observation (*21*).

Treatment of skin disorders

In one case report, administration of 100.0 mg of oil twice daily for 34 days completely healed chronic skin ulcers up to 1 cm deep (*48*).

Adverse reactions

A 60-year-old male was admitted to hospital with neurological and psychotic symptoms following ingestion of 60.0 ml of Oleum Azadirachti.

However, correlation of the adverse effects with ingestion of the oil was not definitely proven (*49*).

Contraindications

Oral administration of Oleum Azadirachti is contraindicated during pregnancy, nursing and in children under the age of 12 years.

Warnings

A number of cases of toxicity, including toxic encephalopathy, poisoning and Reye-like syndrome, following ingestion of excessive doses of Oleum Azadirachti have been reported (*50–52*).

Precautions

Drug interactions

Administration of the oil may reduce blood glucose levels. It should therefore be used with caution in insulin-dependent diabetic patients or patients taking oral antihyperglycaemic drugs.

Carcinogenesis, mutagenesis, impairment of fertility

An acetone extract of the oil was inactive at concentrations of up to 200.0 mg/plate in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98 and TA100 (*53*). In the same test, the oil (concentration not specified) was not mutagenic using *Salmonella typhimurium* strains TA98 and TA100, with or without metabolic activation (*54*).

The oil has demonstrated antifertility effects in numerous animal and human studies (see Pharmacology).

Pregnancy: teratogenic effects

The oil had embryotoxic effects after vaginal administration to pregnant rats at a dose of 0.25 ml/animal (*32, 33*). Embryotoxic effects were also reported following intragastric administration of 4.0 ml/kg bw of the oil to pregnant rats on days 6–8 of pregnancy (*47*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions.

Dosage forms

Oil. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Dose: 1.0–5.0 ml of oil for intravaginal applications (*20, 22*).

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Flos Carthami

Definition
Flos Carthami consists of the dried flowers of *Carthamus tinctorius* L. (Asteraceae) (*1–3*).

Synonyms
Asteraceae are also known as Compositae.

Selected vernacular names
American saffron, baharman, barre, bastard saffron, benibana, biri, centurakam, chôm pu, dok kham, dyer's saffron, esfer, fake saffron, false saffron, hong hoa, hong hua, hong-hua, honghua, huang hua, hung hua, hung-hua, Hungarian saffron, ik-kot, Indian safflower, kafishah, kajirah, karizeh, kazirah, kanar, kasube, kasubha, kasumba, kembang pulu, kham, kham foi, kham yong, khoinbo, kouranka, kusum, kusuma, kusumba, kusumphul, lago, qurtum, rum, saff-flower, safflower, saflor, safran bâtard, sáfrányos szeklice, saffron, saffron thistle, Saflor, senturakam, shawrina, sufir, usfur, wild saffron, za'afran (*3–8*).

Geographical distribution
Indigenous to the Arabian peninsula, north-west India and Islamic Republic of Iran; also found in the Mediterranean region of North Africa and in Cambodia, China, India, Indonesia, Lao People's Democratic Republic and Viet Nam. Widely cultivated around the world (*4, 6, 9–11*).

Description
An annual herb, 0.4–1.3 m high, much branched, glabrous, spiny. Branches stiff, cylindrical, whitish in colour. Leaves simple, spirally arranged, without petiole; oblong, ovate, lanceolate or elliptic; dark green, glossy, 3–15 cm long, 1.5 cm wide, spinous along the margin and at the tip. Flowers solitary, terminal, 2.5–4.0 cm in diameter with spreading outer leafy spiny bracts and inner triangular bracts, spine tipped, forming a conical involucre, with small opening at the tip. Florets, 30–90, tubular,

hermaphrodite, usually orange-yellow in colour; corolla tubes 4 cm long, with five pointed segments. Fruits white or grey, tetragonal achenes, about 8 mm long, without pappus (*6*).

Plant material of interest: dried flowers

General appearance

Red to red-brown corollas, yellow styles and stamens, rarely mixed with immature ovaries; corollas tubular, 1–2 cm long, with five segments; long pistils surrounded by five stamens; pollen grains yellow and spherical, approximately 50.0 µm in diameter, with fine protrusions on the surface (*1–3*).

Organoleptic properties

Odour: characteristic aromatic; taste: slightly bitter (*1–3*).

Microscopic characteristics

Information to be developed according to national requirements.

Powdered plant material

Orange-yellow with fragments of corolla, filament and stigma. Long tubular secretory cells, up to 66 µm in diameter, usually accompanied by vessels containing yellowish-brown to reddish-brown secretion. Outer walls of terminal epidermal cells of corolla lobes projecting to be tomentellate. Upper epidermal cells of stigma and style differentiated into conical unicellular hairs, acuminate or slightly obtuse at the apex. Pollen grains subrounded, elliptical or olivary, with three germinal pores, exine dentate spinose. Parenchymatous cells containing crystals of calcium oxalate, 2–6 µm in diameter (*3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), microchemical tests, spectrometry (*1–3*), and thin-layer chromatography (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 2% (*1–3*).

Total ash
Not more than 18% (*1, 2*).

Loss on drying
Not more than 13% (*3*).

Pesticide residues
The recommended maximum limit for the sum of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

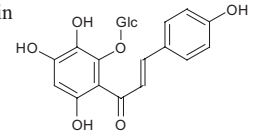
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

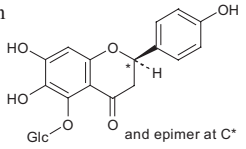
Chemical assays
To be established in accordance with national requirements. A high-performance liquid chromatography method for analysis of carthamin, safflor yellow A and other related pigments is available (*15*).

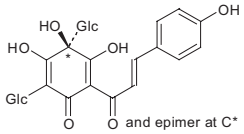
Major chemical constituents
The major constituent is the chalcone C-glucoside carthamin (up to 8.5%) (*16*). Other significant constituents include fatty acids, the chalcone hydroxysafflor yellow A; the nitrogenous chalcone tinctormine; the quinoid C-glycosides safflor yellow A and safflor yellow B; the flavonoids neocarthamin, quercetin, rutin, kaempferol and related hydroxy derivatives and glycosides; dotriacontane-6,8-diol, erythrohentriacontane-6,8-diol, heptacosane-8,10-diol, triacontane-6,8-diol and related alkanes (*8, 17, 18*). Representative structures of chalcones, quinoid C-glycosides and a flavanone are presented below.

carthamin

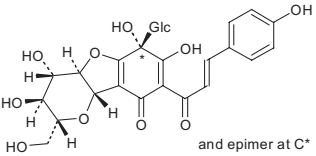


neocarthamin

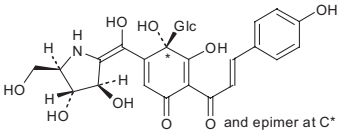




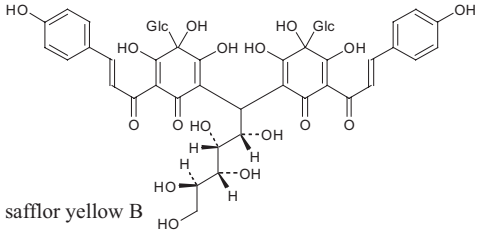
hydroxysafflor yellow A



safflor yellow A

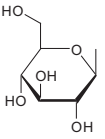


tinctormine



safflor yellow B

β-D-glucopyranosyl Glc =



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Treatment of amenorrhoea, dysmenorrhoea and wounds or sores with pain and swelling, and prevention of atherosclerosis (*3, 19*).

Uses described in traditional medicine

As an antipyretic, antidiarrhoeal, contraceptive, diaphoretic, emmenagogue, expectorant, laxative, sedative and stimulant (*8, 20, 21*). Treatment of bronchitis, boils, haemorrhoids, respiratory tract infections, ringworm and scabies (*8, 20*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500.0 mg/kg body weight (bw) of a 95% ethanol extract of Flos Carthami reduced the responsiveness of mice as measured in the hot-plate test, indicating an analgesic effect, and also

decreased yeast-induced fevers (*22*). Subcutaneous administration of 10.0 g/kg bw of an aqueous extract of the flowers to mice did not reduce pain perception as measured in the hot-plate test (*23*). However, subcutaneous administration of 1.0–3.0 g/kg bw of a 50% methanol extract of the flowers to mice reduced writhing induced by acetic acid (*23*). Intragastric administration of 30.0 g/kg bw of a 50% methanol extract of the flowers to mice also reduced writhing induced by acetic acid (*24*).

Antihepatotoxic activity

Intraperitoneal injection of a methanol extract of 100.0 mg/kg bw of the flowers to rats reduced the increased activities of alkaline phosphatase, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase and lactate dehydrogenase, and reduced the plasma concentration of bilirubin in hepatotoxicity induced by the administration of α-naphthylisothiocyanate (*25*). However, intraperitoneal administration of 300.0 mg/kg bw of a methanol extract of the flowers to rats had no effect on hepatotoxicity induced by carbon tetrachloride (*26*). Conversely, administration of the flowers to rats prevented the development of liver cirrhosis induced by carbon tetrachloride in eight out of nine animals. In the control group, seven out of nine rats developed cirrhosis when treated with carbon tetrachloride (*27*).

Anti-inflammatory activity

Intragastric administration of 30.0 mg/kg bw of a 50% methanol extract of the flowers inhibited inflammation as measured by footpad oedema in mice, induced by carrageenan, serotonin, bradykinin, histamine or prostaglandin (*24*). Subcutaneous administration of 10.0 g/kg bw of an aqueous or 50% methanol extract of the flowers inhibited carrageenan-induced footpad oedema in mice (*23*).

In vitro, 1-butanol and petroleum ether extracts of the flowers had albumin-stabilizing effects, indicating anti-inflammatory activity; however, the aqueous extract was not active in this assay (*28*).

Antimicrobial activity

An ethanol extract of the flowers inhibited the growth of *Staphylococcus aureus* in vitro at a concentration of 0.5 mg/plate, but was not effective against *Escherichia coli* (*29*). A 95% ethanol extract of the flowers inhibited the growth of *Bacillus subtilis, Candida albicans, Salmonella typhosa* and *Staphylococcus aureus* in vitro at a concentration of 100.0 µg/plate, but was not effective against *E. coli* and *Shigella dysenteriae* (*30*). A hot aqueous extract of the flowers (concentration not specified) inhibited replication of poliomyelitis virus type 1 in vitro (*31*).

Cardiovascular effects

Intragastric administration of 4.0 g/kg bw of a 50% methanol extract of the flowers to male rats did not reduce congestive oedema induced by bilateral ligation of the jugular vein (*32*). Intravenous administration of 2.0 g/kg bw of a decoction of the flowers to dogs reduced ST-segment elevation and the increased heart rate induced by occlusion of the apical branch of the coronary artery (*33*). Intraperitoneal administration of a hot aqueous extract of 10.0 g/kg bw of the flowers to gerbils reduced ischaemia and neurological damage induced by unilateral carotid artery ligation when compared with untreated animals (*34*). In vitro, an aqueous extract of the flowers (concentration not specified) displayed calcium-channel blocking activity by displacing nitrendipine or diltiazem from receptor sites (*35*). Tinctormine (concentration not specified) isolated from the flowers, also showed in vitro calcium antagonist activity (*17*).

A 95% ethanol extract of the flowers (dose not specified) induced vasodilation in guinea-pigs and rabbits (*36*). Safflower yellow (containing chalconoid compounds of which 75% is safflomin A) extracted from the flowers (dose not specified) lowered blood pressure in spontaneously hypertensive rats; 5 weeks later, the plasma renin activity and angiotensin II levels were reduced in these animals, suggesting that the reduction in blood pressure was mediated by the renin-angiotensin system (*37*). An aqueous extract of the flowers, 10.0 µg/ml, inhibited the activity of stress-activated protein kinases from isolated ischaemic rat hearts by 50%; when the isolated hearts were treated prior to the induction of ischaemia, the inhibition was 95% (*38*).

Central nervous system depressant activity

Subcutaneous administration of 1.0–10.0 g/kg bw of an aqueous or 50% methanol extract of the flowers had central nervous system depressant effects in mice and relaxed skeletal muscles (*23*). Intraperitoneal administration of 500.0 mg/kg bw of a methanol extract of the flowers per day for 3 days did not potentiate barbiturate-induced sleeping time in mice (*39*). Subcutaneous administration of 10.0 g/kg bw of a 50% methanol extract of the flowers inhibited pentylenetetrazole-induced convulsions in mice (*23*).

Immune system effects

Intraperitoneal administration of 50.0–450.0 mg/kg bw of safflower yellow extracted from the flowers per day for 6 days suppressed antibody formation in mice (*40*). Intraperitoneal administration of 50.0 mg of an aqueous extract of the flowers per day for 6 days to mice delayed cutaneous hypersensitivity reactions, demonstrating immune suppressant activ-

ity. Administration of the extract resulted in decreased lysozyme concentrations, decreased phagocytosis of macrophages and leukocytes, and diminished production of plaque-forming cells, rosette-forming cells, and antibodies. The extract also delayed the responsiveness and activation of T-suppressor lymphocytes (*40*).

Platelet aggregation inhibition

Intraperitoneal administration of 30.0 mg of an aqueous extract of the flowers to mice reduced platelet aggregation induced by adenosine diphosphate (ADP) by 65% in γ-irradiated animals (*41*). Intraperitoneal administration of 0.1 g/kg bw of an ethyl acetate or aqueous extract of the flowers to mice had no effects on platelet aggregation (*42*).

An aqueous extract of the flowers, 2.27 mg/ml, inhibited ADP-induced platelet aggregation by 24.7% in platelets isolated from irradiated rabbits (*41*). Aqueous, hexane and 90% ethanol extracts of the flowers, 5.0 mg/ml, inhibited platelet aggregation induced by ADP, arachidonic acid and collagen in rat platelets (*43*).

Uterine stimulant effects

Intraperitoneal administration of a hot aqueous extract of the flowers (dose not specified) increased uterine contractions in pregnant female rats (*31*).

Toxicology

Intragastric or subcutaneous administration of 10.0 g/kg bw of a 50% ethanol extract of the flowers to mice had no toxic effects (*44*). The intraperitoneal median lethal dose (LD_{50}) of a decoction of the flowers in mice was 1.2 g/kg bw (*19*). The intravenous LD_{50} of a 50% ethanol extract of the flowers in mice was 5.3 g/kg bw. The intravenous and oral LD_{50} values of carthamin in mice were 2.35 g/kg bw and > 8.0 g/kg, respectively. No toxic effects or death of animals was reported after intraperitoneal administration of 12.5 g/kg of a decoction of the flowers per day for 2 days to mice. Chronic administration of 0.015–1.5 g/kg bw of carthamin in the diet per day for 3 months had no toxic effects on the heart, liver, kidneys or gastrointestinal tract of young rats (*19*).

Clinical pharmacology

No information available.

Adverse reactions

Increased menstrual flow may occur (*19*). Dizziness, skin eruptions and transient urticaria have been reported (*19*).

Contraindications

Owing to its traditional use as an emmenagogue and its stimulatory effects on the uterus, Flos Carthami should not be administered during pregnancy. Flos Carthami is also contraindicated in haemorrhagic diseases, peptic ulcers and excessive menstruation (*19*).

Warnings

No information available.

Precautions

Drug interactions

Although no drug interactions have been reported, extracts of Flos Carthami inhibit platelet aggregation (*41, 43*). The flowers should therefore be used with caution in patients taking anticoagulants or antiplatelet drugs.

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous or methanol extract of the flowers was not mutagenic in concentrations up to 100.0 mg/ml in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with liver microsomes (*45, 46*). An aqueous or methanol extract of the flowers, 100.0 mg/ml, was not mutagenic in the *Bacillus subtilis* recombination assay (*45*). However, other investigators have reported that aqueous extracts of the flowers were mutagenic at concentrations of 50.0 µg/ml and 5.0 mg/plate in *S. typhimurium* strains TA98 and TA100 (*29, 47*). Intraperitoneal administration of 4.0 g/kg bw of an aqueous extract of the flowers to mice was mutagenic (*46*).

Intragastric administration of 240 mg of an aqueous extract of the flowers to female rats had no effects on fetal implantation and no embryotoxic effects (*8*). Intragastric administration of 2.0 g/kg bw of an aqueous extract of the flowers twice per day to female rats throughout pregnancy had no effect on implantation, gestation or duration of fetal expulsion, but did cause fetal loss by resorption (*48*).

Pregnancy: teratogenic effects

Pregnant mice were treated with varying doses of an aqueous extract of the flowers during days 0–8 of gestation, and the embryos were isolated and evaluated on day 13 of the gestational period. The results showed that, at doses of 1.6 mg/kg bw and 2.0 mg/kg bw per day, the extract induced embryo absorption, while at 1.2 mg/kg bw per day, changes in the

external, internal and longitudinal diameters, open neuropore, cellular orientation and cellular degeneration were observed (*49*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
No information available. However, owing to possible mutagenic effects, use of Flos Carthami during nursing should be only on the advice of a health-care professional.

Paediatric use
No information available. However, owing to possible mutagenic effects, use of Flos Carthami in children should be only on the advice of a health-care professional.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions.

Dosage forms
Dried flowers for infusions and decoctions; extracts. Store in a cool dry place protected from moisture (*3*).

Posology
(Unless otherwise indicated)
Average daily dose: 3.0–9.0 g of Flos Carthami as an infusion or decoction; equivalent for other preparations (*2, 3*).

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Stigma Croci

Definition
Stigma Croci consists of the dried stigmas of *Crocus sativus* L. (Iridaceae) (*1, 2*).

Synonyms
Crocus officinalis Martyn (*3*).

Selected vernacular names
Açcfrão, azaferan, azafran, crocus, crocus hispanicus, crocus orientalis, dye saffron, Echter Safran, fan-hung-hua, Gewürzsafran, hay saffron, kamkana, kesar, keshara, koema-koema, kumkum, Safran, saffraon, saffron, saffron crocus, sáfrány, sapran, Spanish saffron, true saffron, szafran, szafrana, z'afaran, za afran l-hor, zaafaran, zafaran, zafarfon, zafferano, zang hong hua, zafrane hor (*1–6*).

Geographical distribution
Indigenous to southern Europe and south-western Asia. Cultivated in the Eastern Mediterranean and in China, France, India, Italy and Spain (*4, 5*).

Description
A perennial, low growing (8–30 cm high), bulbous herb with an underground globular corm, producing six to nine sessile leaves, surrounded in its lower part by four or five broad membranous scales. Flowers borne on the terminal region of a scape, each flower consisting of a pale reddish-purple perianth showing a cylindrical tube about 10 cm long and six oblong oval segments, an androecium of three stamens and a gynoecium of three syncarpous carpels. Ovary inferior, three-locular. Style slender, elongated and pale yellow in the perianth tube, divided in its upper part into three drooping, deep-red stigmas (*4, 7*).

Plant material of interest: dried stigmas

General appearance

Thin cord-like stigmas, dark yellow-red to red-brown, 1.5–3.5 cm long, tripartite or separate, the upper part broader and slightly flattened, the distal end split longitudinally and rolled into a slender funnel with a crenate edge. Margin of the apex irregularly dentate, with a short slit at the inner side, sometimes with a small piece of style remaining at the lower end. Texture light, lax and soft, without oily lustre (*1, 2, 8*).

Organoleptic properties

Odour: characteristic, aromatic, slightly irritant; taste: pungent, slightly bitter (*1, 2, 8*).

Microscopic characteristics

When softened by immersion in water, upper ends of the stigmas show numerous tubular protrusions about 150 µm long, with a small number of pollen grains, which are spherical, smooth and without spines (*1, 9, 10*).

Powdered plant material

Orange-red. Epidermal cells long, thin-walled, slightly sinuous, stripe-shaped in the surface view; outer walls sometimes protrude, showing papillae, with indistinct fine striations. Terminal epidermal cells of stigma are papillose, 26–56 µm in diameter, with sparse striations on the surface. Parenchymatous cells are crowded with round-fascicle, fusiform or subsquare granular crystals of calcium oxalate, 2–14 µm in diameter (*2*).

General identity tests

Macroscopic and microscopic examinations, microchemical and spectrophotometric tests (*1, 2*), and thin-layer chromatography (*11*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Total ash

Not more than 7.5% (*1, 2*).

Loss on drying

Not more than 12.0% (*1, 2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, foreign organic matter, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Colorimetric (*1*) and spectrophotometric (*2*) assays are used. Qualitative and quantitative high-performance liquid chromatography methods are available for picrocrocin, safranal and crocins (*15–17*).

Major chemical constituents

The major constituents include essential oils (0.4–1.3%) with α- and β-pinene, 1,8-cineole (eucalyptol), a monoterpene glucoside, picrocrocin (4%), safranal, which can be obtained by hydrolysis of picrocrocin, and a series of carotenoid glucosides known as crocins (2%), dimethylcrocetin and their aglycone crocetin (*3, 8*). Representative structures are presented below.

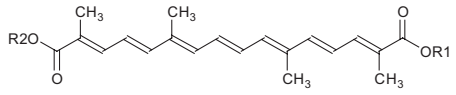
Medicinal uses

Uses supported by clinical data

None. Although Stigma Croci showed antioxidant effects in human studies (*18*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

As a tonic and antiarteriosclerotic (*19, 20*), and as a sedative and emmenagogue (*2, 5, 21*).



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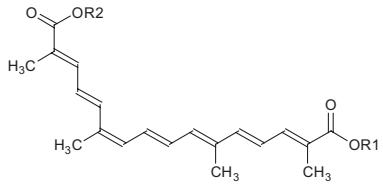
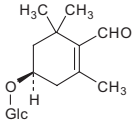
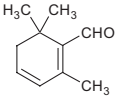
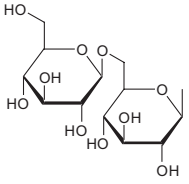


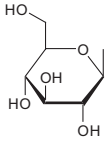
	R1	R2
α-crocetin (crocetin)	H	H
β-crocetin	H	CH_3
and	CH_3	H
γ-crocetin (dimethylcrocetin)	CH_3	CH_3
A-crocin (crocin)	Gen	Gen
B-crocin (crocin 2)	Gen	Glc
and	Glc	Gen
C-crocin (crocin 3)	Gen	H
and	H	Gen
D-crocin (crocin 4)	Glc	Glc
E-crocin	Glc	H
and	H	Glc

picrocrocin 

safranal 

gentiobiosyl :

6–O–β-D-glucopyranosyl-
β-D-glucopyranosyl | Gen = 

β-D-glucopyranosyl | Glc = 

Uses described in traditional medicine

As an emmenagogue and for treatment of ammenorrhoea, abdominal pain, coughs, depression, digestive ailments, fever and pain due to wounds (*22, 23*). Also as an aphrodisiac, appetite stimulant, diaphoretic, contraceptive, antispasmodic and nerve sedative (*6, 22*).

Pharmacology

Experimental pharmacology

Antiarteriosclerotic effects

Administration of a monthly intramuscular injection of crocetin (dose not specified) to rabbits fed an atherosclerosis-inducing diet reduced serum cholesterol concentrations by 50%, and reduced the severity of atherosclerosis by ~30% (*24*).

Anticoagulant activity

A hot aqueous extract of Stigma Croci, 10–100.0 mg/ml, prolonged partial thromboplastin and prothrombin times, and inhibited platelet aggregation in human platelets induced by adenosine diphosphate and collagen in vitro (*25*).

Cell proliferation inhibition

Treatment of cervical epitheloid carcinoma (HeLa) cells with a concentrated extract (undefined) of the stigmas, 50.0–150.0 µg/ml, for 3 hours

inhibited colony formation by 25% and decreased the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) by 50% in vitro (*26, 27*).

Crocin and crocetin, 0.8–2.0 µmol/l, isolated from an extract of the stigmas, inhibited the growth of human acute promyelocytic leukaemia cells in vitro (*28*). Crocetin, 35–55.0 µg/ml, inhibited the synthesis of nucleic acids and protein in cervical epitheloid carcinoma, lung carcinoma and transformed fetal fibroblast malignant human cell lines (*29*). Incubation of cervical epitheloid carcinoma cells (HeLa), lung adenocarcinoma cells (A549) and SV-40 transformed fetal lung fibroblast cells with varying concentrations of crocetin for 3 hours resulted in a dose-dependent reduction in DNA and RNA synthesis, and suppression of RNA polymerase II activity (*26*).

Central nervous system effects

Intragastric administration of 125–250.0 mg/kg body weight (bw) of a 50% ethanol extract of the stigmas had a tranquillizing effect in mice, and potentiated the sedative effects of barbiturates (*30*).

Chemical carcinogenesis inhibition

Topical application of 100 mg/kg bw of a 95% ethanol extract of the stigmas inhibited two-stage initiation and promotion of skin carcinogenesis in mice, delaying the onset of papilloma formation and reducing the mean number of papillomas per mouse (*31*). Intragastric administration of 100.0 mg/kg bw of the same extract per day for 30 days reduced the incidence of soft tissue sarcomas induced by 20-methylcholanthrene by 10% in mice (*31*). Intragastric administration of 100.0 mg/kg bw of an ethanol extract of the stigmas to mice inhibited the growth of solid Dalton lymphoma ascites and sarcoma 180 tumours by 87% and 41%, respectively (*23, 32*). Subcutaneous administration of 400.0 mg/kg bw of crocin weekly for 13 weeks, slowed the growth of colon adenocarcinoma and increased the lifespan of female but not male mice (*33*).

Intraperitoneal administration of 50 mg/kg bw of a 95% ethanol extract of the stigmas to mice partially prevented the decreases in body weight, haemoglobin levels and leukocyte counts caused by cisplatin treatments (*32*).

Circulation effects

External application of a 1% aqueous solution containing crocin analogues isolated from *Crocus sativus* significantly ($P < 0.05$) increased blood flow to the retina and choroid in rabbits with ocular hypertension. Intraperitoneal administration of 10.0 mg/kg bw of crocin analogues to rats facili-

tated the recovery of retinal function after induction of retinal ischaemia by occlusion of the central retinal and posterior ciliary arteries (*34*).

Cytotoxicity

In vitro, crocin had potent cytotoxic effects on human and animal adenocarcinoma cells, with median lethal doses (LD_{50}) of 0.4 mmol/l and 1.0 mmol/l, respectively (*33*). An aqueous extract of the stigmas (LD_{50} 2.3 mg/ml), crocin (LD_{50} 3 mmol/l), picrocrocin (LD_{50} 3 mmol/l) and safranal (LD_{50} 0.8 mmol/l) inhibited the growth of HeLa cells in vitro. The cells treated with crocin exhibited wide cytoplasmic vacuole-like areas, reduced cytoplasm and cell shrinkage, indicating the induction of apoptosis (*35*).

Nootropic effects

An unspecified alcohol extract of the stigmas enhanced learning and memory in learning-impaired mice (*36*). Intragastric administration of 125.0–500.0 mg/kg bw of the extract did not affect learning behaviours in normal mice, but prevented ethanol-induced learning impairment, and prevented ethanol-induced inhibition of hippocampal long-term potentiation (a form of activity-dependent synaptic plasticity that may support learning and memory) in anaesthetized rats (*30, 36*). Intragastric administration of a single dose of 250.0 mg/kg bw of the same extract prevented acetaldehyde-induced inhibition of long-term potentiation in the dentate gyrus of anaesthetized rats (*37*). In a follow-up study, treatment of mice with an ethanol extract of 250.0 mg/kg bw of the stigmas improved ethanol-induced impairments of learning behaviours in mice and prevented ethanol-induced inhibition of hippocampal long-term potentiation (*38*). The effect was attributed to crocin, but not crocetin.

Toxicity

The LD_{50} for Stigma Croci was reported to be 20.7 g/kg bw in rodents (*23*). The LD_{50} of a 95% ethanol extract of the stigmas was > 600 mg/kg bw in mice (*39*). Mice treated with dimethylcrocetin isolated from the stigmas did not exhibit haematological or biochemical toxic effects after intragastric administration of up to 50.0 mg/kg bw (*23*).

Clinical pharmacology

The antioxidant effects of the stigmas were assessed in a clinical trial involving 30 subjects in three groups: 10 healthy volunteers, 10 patients with coronary artery disease and 10 healthy controls. The two test groups received 50 mg of Stigma Croci in 100.0 ml of milk twice daily for 6 weeks, the controls received milk only. Lipoprotein oxidation in blood samples

decreased by 42.3% in healthy volunteers ($P < 0.001$) and 37.9% ($P < 0.01$) in patients with coronary artery disease compared with controls (*18*).

Adverse reactions

The lethal dose of Stigma Croci is reported to be 20.0 g; however, smaller doses may cause vomiting, uterine bleeding, bloody diarrhoea, haematuria, bleeding from the nose, lips and eyelids, vertigo, numbness and yellowing of the skin and mucous membranes (*5*). Oral administration of 5.0 g resulted in localized skin haemorrhages, marked thrombocytopenia, and abnormalities of blood clotting in one patient (*40*).

Contraindications

Stigma Croci may induce uterine contractions and is therefore contraindicated during pregnancy (*5*). Owing to a lack of safety data, use of the stigmas in children and nursing mothers should be restricted to normal food use. Stigma Croci is contraindicated in bleeding disorders.

Warnings

At doses of 5.0 g or more, Stigma Croci may cause serious adverse reactions (see Adverse reactions). Overdose of Stigma Croci (12.0–20.0 g/day) may be fatal (*7, 22*).

Precautions

Drug interactions

Stigma Croci inhibits platelet aggregation and should therefore be used with caution in patients taking anticoagulant or antiplatelet drugs.

Carcinogenesis, mutagenesis, impairment of fertility

Ethyl acetate, methanol and aqueous extracts of Stigma Croci (concentrations not specified) were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation (*41*). Crocin and dimethylcrocetin,1.0 mg/plate, 2.0 mg/plate and 4.0 mg/plate, were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA 1535 (*23*). A chloroform-methanol extract (2:1) of the stigmas, 100.0 mg/plate, was not mutagenic in pig kidney cells or in trophoblastic placenta cells (*42*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms
Dried stigmas; extracts of dried stigmas. Store the dried stigmas in a tightly sealed metal or glass container, protected from light and moisture (*5*).

Posology
There is insufficient information available to give an accurate assessment of dose range. No risk is associated with consumption in standard food use quantities (*22, 43*). The recommended therapeutic daily dose is 3.0–9.0 g (*2*). However, owing to a report of toxicity at 5.0 g (*40*), doses below 5.0 g/day are recommended.

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Fructus Foeniculi

Definition

Fructus Foeniculi consists of the dried ripe fruits of *Foeniculum vulgare* Mill. (Apiaceae) (*1–8*).[1]

Synonyms

Anethum foeniculum Clairv., *A. foeniculum* L., *A. rupestre* Salisb., *Feniculum commune* Bubani, *Foeniculum azoricum* Mill., *F. capillaceum* Gilib., *F. dulce* DC., *F. foeniculum* (L.) H. Karst., *F. officinale* All., *F. panmorium* DC., *F. piperitum* DC., *F. sativum* Bertol, *Ligusticum divaricatum* Hoffmannsegg et Link, *L. foeniculum* Crantz, *Meum foeniculum* (L.) Spreng., *Ozodia foeniculacea* Wight et Arn., *Selinum foeniculum* (L.) E.H.L. Krause (*2, 3, 9, 10*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aneth doux, arap saçi, besbes, bitter fennel, Bitterfenchel, brotanis, common fennel, dill, édeskömény, erva doce, fãnksal, fannel, Fencel, Fenchel, fenchul, Fennekel, fennel, Fennichl, fennikel, Fennkol, fenouil, fenucchiello, fenucchio, fenykl, finkel, Finkel, finichio, finocchio, finucco, fiolho, florence fennel, foenoli doux, funcho, gemeiner Fenchel, Gemüsefenchel, giant fennel, guvamuri, hierba de anis, hinojo, hui-hsiang, imboziso, insilal, koper wloski, lady's chewing tobacco, large fennel, madesi souf, madhurika, marathoron, maratrum, marui, misi, nafa, panmauri, razianeh, razianaj, sanuf, shamar, shomar, sladkij ukrop, sohoehyang, sopu, spingel, sup, thian khaao phlueak, thian klaep, venkel, sweet fennel, uikyo, uikyou, vegetable fennel, vinkel, wild fennel, xiao hui, xiaohuixiang, yi-ra (*2, 3, 6, 8, 9, 11–14*).

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[1] The *European pharmacopoeia* (*7*) recognizes *Foeniculum vulgare* Mill. ssp. *vulgare* var. *vulgare (*Foeniculi amari fructus, Bitter Fennel) and *F. vulgare* Mill. ssp. *vulgare* var. *dulce (*Foeniculum dulcis fructus, Sweet Fennel) as distinct entities for which separate monographs are provided. However, in the biological literature, a clear delineation at the variety level is generally not made. Therefore, this monograph has not made the distinction between the "bitter" and "sweet" varieties.

Geographical distribution

Indigenous to the Mediterranean region. Cultivated in Europe, Asia and temperate regions of Africa and South America (*2, 12, 15*).

Description

Perennial aromatic herb, 1–3 m high with green, glaucous, furrowed, branched stems bearing alternate leaves, 2–5 times pinnate with extremely narrow leaflets. Superior leaves with sheaths longer than the blade. Umbels compound, large, nearly regular, on long peduncles. Flowers yellow, no involucre; calyx with five very slight teeth; petals five, entire, tips involute; stamens five; ovary two-celled; stylopodium large, conical. Fruit an oblong cremocarp, 6–10 mm long, 1–4 mm in diameter, greenish; glabrous mericarp compressed dorsally, semicylindrical, with five prominent, nearly regular ribs. Seeds somewhat concave, with longitudinal furrows (*3, 15, 16*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp, oblong 3.5–10.0 mm long, 1–3 mm wide, externally greyish yellow-green to greyish yellow often with pedicel 2–10 mm long. Mericarps usually free, glabrous, each bearing five prominent slightly crenated ridges (*1–4, 7, 8*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet to bitter (*1–4, 8*).

Microscopic characteristics

Outer epidermis of the pericarp consists of thick-walled, rectangular, polygonal, colourless cells, with smooth cuticle, few stomata and no hairs. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, appearing elliptical in section and possessing brown epithelial cells; traversed in the ridges by vascular bundles, each having one inner xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres; some of the mesocarp cells, especially those about the vascular bundles, possess lignified, reticulate cells. Endocarp composed of one layer of flattened thin-walled cells varying in length, but mostly 4–6 µm thick, arranged parallel to one another in groups of five to seven. Endosperm, formed of somewhat thick-walled polygonal cellulosic parenchyma containing fixed oil, several aleurone grains (up to 6 µm in diameter) enclosing a globoid, and one or more microrosette crys-

tals of calcium oxalate, about 3 µm in diameter. Carpophore often not split, with thick-walled sclerenchyma in two strands (*2, 8*).

Powdered plant material

Greyish-brown to greyish-yellow. Yellowish-brown-walled polygonal secretory cells, frequently associated with a layer of thin-walled transversely elongated cells 2–9 µm wide, in a parquet arrangement; reticulate parenchyma of the mesocarp; numerous fibre bundles from the ridges, often accompanied by narrow spiral vessels; very numerous endosperm fragments containing aleurone grains, very small microrosette crystals of calcium oxalate, and fibre bundles from the carpophore (*7*).

General identity tests

Macroscopic and microscopic examinations (*1–4, 7, 8*), thin-layer chromatography for the presence of anethole and fenchone (*7*), and gas chromatography for the presence of anethole, fenchone and estragole (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*17*).

Foreign organic matter

Not more than 1.5% peduncles and not more than 1.5% other foreign matter (*4, 7*).

Total ash

Not more than 10% (*1, 4, 7, 8, 18*).

Acid-insoluble ash

Not more than 1.5% (*1, 2, 4*).

Water-soluble extractive

Not less than 20% (*3*).

Alcohol-soluble extractive

Not less than 11% (*3*).

Moisture

Not more than 8% (*7*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*19*). For other pesticides, see the *European pharmacopoeia* (*19*) and the WHO guidelines on quality control methods for medicinal plants (*17*) and pesticide residues (*20*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*17*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*17*) for the analysis of radioactive isotopes.

Other purity tests

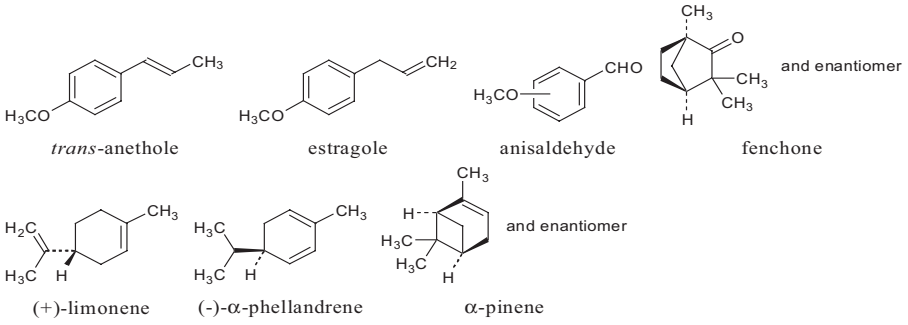
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 1.4% v/w essential oil (*1, 2, 4, 6*).

Major chemical constituents

The major constituent is the essential oil (2–6%), which contains *trans*-anethole (50–82%), (+)-fenchone (6–27%), estragole (methylchavicol) (3–20%), limonene (2–13%), *p*-anisaldehyde (6–27%), α-pinene (1–5%) and α-phellandrene (0.1–19.8%) (*9, 12, 14, 21, 22*). Representative structures are presented below.



trans-anethole estragole anisaldehyde fenchone

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of dyspepsia, bloating and flatulence (*9, 23–25*). As an expectorant for mild inflammation of the upper respiratory tract (*24, 26*). Treatment of pain in scrotal hernia, and dysmenorrhoea (*8*).

Uses described in traditional medicine

Treatment of blepharitis, bronchitis, constipation, conjunctivitis, diabetes, diarrhoea, dyspnoea, fever, gastritis, headache, pain, poor appetite and respiratory and urinary tract infections (*14*). As an aphrodisiac, anthelminthic, emmenagogue, galactagogue and vermicide (*14, 27, 28*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of Fructus Foeniculi to mice reduced the perception of pain as measured in the hot-plate test, and decreased yeast-induced pyrexia (*29*). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats had significant ($P < 0.05$) analgesic activity in the hot-plate reaction test (*30*). In mice with yeast-induced pyrexia, treatment with 500.0 mg/kg bw of the same extract reduced rectal temperature from 36.5 °C to 34.7 °C 90 minutes after administration (*30*).

Antimicrobial activity

An essential oil from the fruits inhibited the growth of *Alternaria* species, *Aspergillus flavus, A. nidulans, A. niger, Cladosporium herbarum, Cunninghamella echinulata, Helminthosporium saccharii, Microsporum gypseum, Mucor mucedo, Penicillium digitatum, Rhizopus nigricans, Trichophyton roseum* and *T. rubrum* in vitro (*31, 32*). In another study, an essential oil was not active against *Aspergillus* species in vitro but a methanol extract of the fruits inhibited the growth of *Helicobacter pylori* (the bacterium associated with gastritis and peptic ulcer disease) in vitro, minimum inhibitory concentration 50.0 µg/ml (*33*). An essential oil from the fruits inhibited the growth of *Candida albicans, Escherichia coli, Lentinus lepideus, Lenzites trabea, Polyporus versicolor, Pseudomonas aeruginosa* and *Staphylococcus aureus* (*34*), and *Kloeckera apiculata, Rhodotorula rubra* and *Torulopsis glabrata* (*35*) in vitro. An ethyl acetate extract of the seeds inhibited the growth of *Shigella flexneri* (*36*), and an 80% ethanol extract of the seeds inhibited the growth of *Bacillus subtilis* and *Salmonella typhi* at concentrations of 250.0 µg/ml in vitro (*37*).

Antispasmodic activity

An ethanol extract of the fruits, 2.5–10.0 ml/l, 1 part fruits:3.5 parts 31% ethanol, inhibited acetylcholine- and histamine-induced guinea-pig ileal contractions in vitro (*23*). An essential oil from the fruits reduced intestinal spasms in mouse intestine, and was 26% as active as papaverine (*38*). Intragastric administration of 2.0–3.0 g/kg bw of an infusion of the fruits to cats inhibited acetylcholine- and histamine-induced ileum spasms by 50% (*39*). An essential oil from the fruits, 25.0 µg/ml and 10.0 µg/ml, respectively, inhibited oxytocin- and prostaglandin E_2-induced contractions of isolated rat uterus and reduced the frequency of the latter but not the former (*40*).

Cardiovascular effects

Intravenous administration of a 50% ethanol extract of the fruits (dose not specified) reduced blood pressure in dogs (*41*). An aqueous extract of the fruits, 10% in the diet, reduced blood pressure in rats. The effect was abolished by pretreatment of the animals with atropine (*42*). An unspecified extract of the seeds had diuretic effects in rabbits after intragastric administration. The effect was blocked by pretreatment of the animals with morphine (*43*).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats induced diuresis. The effect was comparable to that observed in animals treated with 960.0 mg/kg bw of urea, and was almost double that in controls (*30*).

Estrogenic and antiandrogenic activities

Intragastric administration of 2.5 mg/kg bw of an acetone extract of the seeds daily for 15 days to male rats decreased the protein concentration in the testes and vas deferens, and increased it in the seminal vesicles and prostate gland (*44*). The same dose of the same extract administered to female rats daily for 10 days increased the weight of the mammary glands, while higher doses induced vaginal cornification, increased the weight of the oviduct, endometrium, myometrium, cervix and vagina, and induced estrus (*44*). A follow-up study demonstrated that the acetone extract induced cellular growth and proliferation of the endometrium, and stimulated metabolic changes in the myometrium of rats. These changes appeared to favour the survival of spermatocytes and the implantation of the zygote in the uterus (*45*). Conversely, intragastric administration of 2.0 g/kg bw of an aqueous extract of the seeds per day for 25 days significantly ($P < 0.025$) reduced female fertility in mice compared with controls. No effect was observed in male mice (*46*).

Intragastric administration of 0.5 mg/kg bw or 2.5 mg/kg bw of an acetone extract of the fruits per day for 10 days to ovariectomized female rats had estrogenic effects (*45*). Intragastric administration (dose not specified) of an essential oil from the fruits to goats increased the amount of milk produced and the fat content of the milk (*47*). Lactating mice fed the fruits in the diet (concentration not specified) produced pups that ate a larger quantity of fennel-containing foods, suggesting that the constituents of the fruits may be passed in breast milk (*48*). Intragastric administration of 250.0 mg/kg bw of unspecified extracts of the fruits induced estrus and increased the size of the mammary glands and oviducts in adult ovariectomized rats, and exerted an antiandrogenic effect in adult male mice. It also increased the weight of the cervix and vagina of ovariectomized rats, and increased the concentration of nucleic acids and protein in cervical and vaginal tissues. The hyperplasia and hypertrophy of the cervix and vagina were similar to changes seen during estrus in normal female rats (*45*).

Subcutaneous administration of anethole (dose not specified) to sexually immature female rats increased uterine weight and induced estrus. However, in ovariectomized mice the same treatment was not estrogenic (*49*). Intramuscular injection of 100.0 mg/kg bw or 500.0 mg/kg bw of anethole per day for 7 days to rats induced a significant decrease in dorsolateral prostate weight ($P < 0.05$) (*50*). Intragastric administration of 50.0 mg/kg bw, 70.0 mg/kg bw or 80.0 mg/kg bw of *trans*-anethole to rats had anti-implantation effects, with the maximum effect (100%) at the highest dose (*51*). The compound showed estrogenic effects, and did not demonstrate anti-estrogenic, progestational or androgenic effects (*51*).

Expectorant and secretolytic effects

Application of an infusion of Fructus Foeniculi, 9.14 mg/ml, to isolated ciliated frog oesophagus epithelium increased the transport velocity of fluid by 12%, suggesting an expectorant effect (*52*). Administration of 1.0–9.0 mg/kg bw anethole and 1.0–27.0 mg/kg bw fenchone by inhalation to urethanized rabbits produced a decrease in the specific gravity of the respiratory fluid and enhanced the volume output of respiratory tract fluid (*53*).

Gastrointestinal effects

Intragastric administration of 24.0 mg/kg bw of the fruits increased spontaneous gastric motility in unanaesthetized rabbits; at a dose of 25.0 mg/kg bw the fruits reversed the reduction of gastric motility induced by pentobarbital (*54*).

Sedative effects

Intragastric administration of an essential oil from the fruits (dose not specified) to mice reduced locomotor activity and induced sedation (*55*). A single intraperitoneal administration of 200.0 mg/kg bw of an ether extract of the seeds enhanced barbiturate induced sleeping time in mice. However, intragastric administration of 200.0 mg/kg bw of the extract per day for 7 days decreased barbiturate-induced sleeping time (*56*).

Toxicology

Intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the fruits induced piloerection and reduced locomotor activity in mice (*30*). Acute (24-hour) and chronic (90-day) oral toxicity studies with an ethanol extract of the fruits were performed in rodents. Acute doses were 0.5 g/kg, 1.0 g/kg and 3.0 g/kg per day; the chronic dose was 100.0 mg/kg per day. No acute or chronic toxic effects were observed (*57*). The acute median lethal dose (LD_{50}) of anethole in rats was 3.8 mg/kg bw after intragastric administration (*58, 59*). Intragastric or subcutaneous administration of 10.0–16.0 g/kg bw of a 50% ethanol extract of the fruits to mice had no toxic effects (*60*). The oral LD_{50} of an essential oil from the fruits in mice was 1326.0 mg/kg bw (*61*).

Chronic use of high doses of *trans*-anethole in rodent dietary studies has been shown to induce cytotoxicity, cell necrosis and cell proliferation. In rats, hepatotoxicity was observed when dietary intake exceeded 30.0 mg/kg bw per day (*62*). In female rats, chronic hepatotoxicity and a low incidence of liver tumours were reported with a dietary intake of trans-anethole of 550.0 mg/kg bw per day, a dose about 100 times higher than the normal human intake (*62*). In chronic feeding studies, administration of *trans*-anethole, 0.25%, 0.5% or 1% in the diet, for 117–121 weeks had no effect on mortality or haematology, but produced a slight increase in hepatic lesions in the treated groups compared with controls (*63*).

Unscheduled DNA synthesis was not induced in vitro by anethole, but was induced by estragole, an effect that was positively correlated with rodent hepatocarcinogenicity (*64*). However, the dose of estragole used (dose not specified) in the rodent studies was much higher than the dose normally administered to humans. Low doses of estragole are primarily metabolized by *O*-demethylation, whereas higher doses are metabolized primarily by 1'-hydroxylation, and the synthesis of 1'-hydroxyestragole, a carcinogenic metabolite of estragole (*65, 66*).

Clinical pharmacology

No information available.

Adverse reactions

In rare cases, allergic reactions such as asthma, contact dermatitis and rhinoconjunctivitis have been reported in sensitive patients (*67, 68*).

Contraindications

The fruits are contraindicated in cases of known sensitivity to plants in the Apiacaeae (*69, 70*). Owing to the potential estrogenic effects of the essential oil from the seeds and anethole (*44, 45, 50*), its traditional use as an emmenagogue, and the lack of human studies demonstrating efficacy, Fructus Foeniculi should not be used in pregnancy. Pure essential oils should not be given to infants and young children owing to the danger of laryngeal spasm, dyspnoea and central nervous system excitation (*12*).

Warnings

The pure essential oil from the fruits may cause inflammation, and has an irritant action on the gastrointestinal tract.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the fruits, up to 100.0 mg/ml, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with homogenized rat liver microsomes (*71, 72*). Aqueous and methanol extracts of the fruits, up to 100.0 mg/ml, were not mutagenic in the *Bacillus subtilis* recombination assay (*71*). However, a 95% ethanol extract, 10.0 mg/plate, was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102 (*73*). An essential oil from the fruits, 2.5 mg/plate, had mutagenic effects in the *Salmonella*/microsome assay in *Salmonella typhimurium* strain TA100 with metabolic activation (*74*), and in the *Bacillus subtilis* recombination assay (*75*). A similar essential oil had no effects in the chromosomal aberration test using Chinese hamster fibroblast cell lines (*76*).

Pregnancy: teratogenic effects

An essential oil from the fruits, up to 500.0 µg/ml, had no teratogenic effects in cultured rat limb bud cells (*61*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds.

Paediatric use
No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds. See also Contraindications.

Other precautions
No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test reactions.

Dosage forms
Dried fruits, syrup and tinctures. Store the dried fruits in a well-closed container, protected from light and moisture (*7*).

Posology
(Unless otherwise indicated)
Daily dose: fruits 5–7 g as an infusion or similar preparations, higher daily doses (> 7 g fruits) should not be taken for more than several weeks without medical advice (*25*); fennel syrup or honey 10–20 g; compound fennel tincture 5–7.5 g (5–7.5 ml).

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Radix Gentianae Luteae

Definition
Radix Gentianae Luteae consists of the dried roots and rhizomes of *Gentiana lutea* L. (Gentianaceae) (*1–6*).

Synonyms
Asterias lutea Borckh., *Swertia lutea* Vest (*2, 7*).

Selected vernacular names
Bachaka, bachalchaka, balmoney, common gentian, daoua el hoya, esperou, European gentian, felwort, gall weed, gansona, ganssana, Gelber Enzian, genchiana, genciana, genciana amarilla, gentian, gentiana, genziana gialla, genziana maggiore, gentiane, gentiane jaune, grande gentiane, great yellow gentian, jintiana, juntiyana, kaf edheeb, kaf el arnab, kouchâd, kouched, pale gentian, tárnics, wild gentian (*2, 6–10*).

Geographical distribution
Indigenous to mountainous regions of central and southern Europe (*6, 8, 11, 12*).

Description
A perennial herb up to 1.5 m high, with erect rhizomes. Stem thick, hollow, bearing large, opposite, ovate leaves with five to seven nerves and axillary cymes of orange-yellow, open-stellate flowers. Roots beet-like, thickened and branched, starting from a short rhizome. Fruits ovate, capsules containing winged seeds (*2, 8*).

Plant material of interest: dried roots and rhizomes
General appearance
Nearly cylindrical pieces, 3–20 cm long, 2–4 cm in diameter. Rhizome short, with fine, transverse wrinkles, and sometimes with buds and remains of leaves at the upper edge. Root longitudinally and deeply wrin-

kled, and more or less twisted; fractured surface yellow-brown and not fibrous; cambium and its surroundings tinged dark brown (*1, 2, 5*).

Organoleptic properties

Odour: characteristic; taste: initially sweet, becoming persistently bitter (*1, 2, 4, 5*). Bitterness value not less than 10 000 (*4*).

Microscopic characteristics

Transverse section of the root shows a narrow zone of four to six layers of thin-walled cork cells; a cork cambium, a broad zone of secondary cortex with brown, thin-walled parenchyma cells, practically devoid of starch, but containing oil globules and minute acicular crystals; a narrow zone of phloem composed of many layers of collapsed phloem parenchyma and numerous strands of sieve tubes; a distinct cambium; and a broad xylem composed largely of yellowish-brown to yellow, thin-walled wood parenchyma, scattered through which are a few large vessels and some tracheids, isolated or in small groups. Medullary rays indistinct. Transverse section of the rhizome exhibits a similar structure except for islets of sieve tissue in the xylem, a central pith and a collenchymatous phelloderm. Longitudinal sections of rhizome and root exhibit reticulate and scalariform tracheae and tracheids with non-lignified walls (*8*).

Powdered plant material

Moderate yellowish-brown to yellowish-orange. Fragments of reticulate, scalariform and pitted vessels and tracheids; fragments of brownish cork tissue, frequently adhering to which are thick-walled cells, numerous somewhat collapsed, large parenchyma cells; occasional clumps of minute slender prismatic crystals of calcium oxalate (3–6 µm long) in angles of parenchyma cells; starch grains few or absent. Stone cells and fibres absent (*3, 8*).

General identity tests

Macroscopic and microscopic examinations (*1, 2, 4–6*) and microchemical tests (*1, 2, 5*), and thin-layer chromatography (*4, 5*) for detection of adulteration with other *Gentiana* species (*4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter
Not more than 2% (*1, 2*).

Total ash
Not more than 6% (*2, 4, 5*).

Acid-insoluble ash
Not more than 3% (*1, 5*).

Water-soluble extractive
Not less than 33% (*4*).

Loss on drying
Not more than 10% (*1, 2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*4*). For other pesticides, see the *European pharmacopoeia* (*4*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

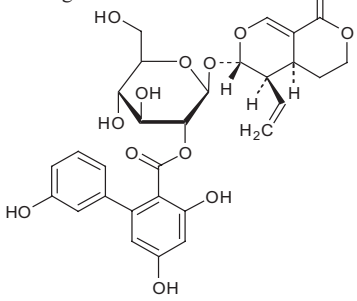
Other purity tests
Chemical, sulfated ash and alcohol-extractive tests to be established in accordance with national requirements.

Chemical assays
High-performance liquid chromatography for the presence of gentiopicroside and amarogentin (*15–17*).

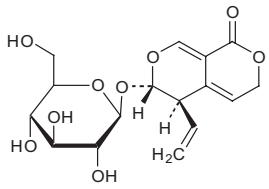
Major chemical constituents
The major constituents are bitter secoiridoid monoterpenes including gentiopicroside (gentiopicrin; 2–8%, sometimes up to almost 10%), swertiamarin, sweroside (0.05–0.08%) and its acylglucoside derivative, amarogentin (0.03–0.08%), which is the bitterest of all compounds in this mat-

erial. Other constituents include xanthones (up to 0.1%), such as gentisin and isogentisin, gentianose (2.5–8.0%) and gentioside, the alkaloid gentianine, and traces of essential oil (*7, 10–12, 18, 19*). Representative structures of the secoiridoid monoterpenes are presented below:

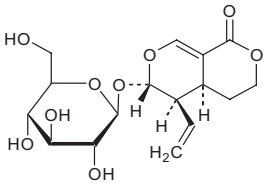
amarogentin



gentiopicroside



sweroside



Medicinal uses

Uses supported by clinical data

None. For the results of three uncontrolled human studies, see Clinical pharmacology (*20–22*). Although the findings suggest that Radix Gentianae Luteae may be of benefit for the treatment of dyspepsia, data from controlled clinical trials are currently lacking.

Uses described in pharmacopoeias and well established documents

Treatment of digestive complaints, such as loss of appetite, feeling of distension and flatulence (*23*). As an appetite stimulant during convalescence (*24*).

Uses described in traditional medicine

As a carminative, depurative, emmenagogue, febrifuge, tranquillizer and tonic, and to facilitate labour (*8, 10*). Treatment of diabetes and dysmenorrhoea (*10*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A 95% ethanol extract of Radix Gentianae Luteae (concentration not specified) inhibited the growth of *Staphylococcus aureus*, but was not active against *Escherichia coli* (*25*). A chloroform extract of the roots and rhizomes, 1.0 g/l, was not active against *S. aureus* (*26*). An aqueous extract of the roots and rhizomes, 500.0 mg/ml, inhibited the growth of the fungi *Aspergillus fumigatus, A. niger, Botrytis cinerea, Fusarium oxysporum* and *Penicillium digitatum* in vitro (*27*).

Antispasmodic activity
A 30% ethanol extract of the roots and rhizomes, 300 mg/l, inhibited acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro (*28*). The essential oil of Radix Gentianae Luteae induced relaxation of smooth muscles in isolated guinea-pig trachea and ileum with median effective doses of 108.0 mg/l and 76.0 mg/l, respectively (*29*).

Choleretic activity
Intragastric administration of a 95% ethanol extract of the roots and rhizomes (dose not specified) to rats was reported to exert a choleretic effect, while an aqueous or methanol extract was not active (*30, 31*). Intraduodenal administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of roots and rhizomes had choleretic effects in rats (*32*).

Secretory activity
Perfusion of a 30% ethanol extract of the roots and rhizomes, 4%, into the stomach of anaesthetized rats increased gastric secretions by 37.0% (*28*). Oral administration of a single dose of 5.0 g of an infusion of the roots and rhizomes to ewes stimulated the secretion of digestive enzymes in the small intestine (*33*).

Intragastric administration of the equivalent of 12.6 mg/kg bw of an alcohol extract of the roots and rhizomes per day for 3 days increased bronchial secretions in treated rabbits as compared with control animals (*34*).

Toxicology
The acute median lethal dose of a 30% ethanol extract of the roots and rhizomes in mice was 25.0 ml/kg (*28*). Intragastric administration of 1.6 ml/kg bw of a combination product containing alcohol extracts of Radix Gentianae, chamomile and liquorice per day for 13 weeks to rats produced no adverse effects and no changes in haemoglobin, red blood cells, packed cell volume, mean corpuscle haemoglobin concentration, total and differential white blood cell count or blood glucose. Histological examination showed no pathological changes in any organ system (*35*). Intragastric administration of 12.6 mg of an alcohol extract of the roots and rhizomes per day (treatment period not specified) to rabbits did not induce any symptoms of toxicity, with the exception of slightly lower erythrocyte concentrations in the treatment group compared with controls (*34*).

Clinical pharmacology
In one study without controls, oral administration of a single dose of 0.2 g of an ethanol extract of the roots 5 minutes prior to a meal

stimulated the secretion of gastric juice (*20*). In the same study, oral administration of 0.2 g of the extract stimulated and prolonged gall bladder secretions as observed by X-ray contrast (*20*). In another uncontrolled clinical trial, 19 patients with colitis ulcerosa, Crohn disease, or other non-specific inflammatory disorders and elevated secretory immune globulin (IgA) concentrations were treated with 20 drops of a tincture of the roots and rhizomes three times per day for 8 days. A control group of healthy volunteers received the same treatment. The IgA levels in both groups dropped and no statistical difference between the two groups was observed (*21*).

A multicentre trial, without controls, assessed the effect of the roots and rhizomes on the symptoms of dyspepsia in 205 patients. Each patient received five capsules containing 120.0 mg of a 5:1 dry ethanol extract of the roots and rhizomes per day. Patients reported relief of symptoms such as constipation, flatulence, appetite loss, vomiting, heartburn, abdominal pain and nausea (*22*).

Adverse reactions

On rare occasions, headaches may occur (*23*).

Contraindications

Owing to potential mutagenic activity (*36–38*), and its traditional use as an emmenagogue (*10*), Radix Gentianae Luteae should not be administered during pregnancy or nursing, or to small children. Radix Gentianae Luteae is contraindicated in gastric or duodenal ulcer, high blood pressure (*11*) and hyperacidity (*7, 24*).

Warnings

No information available.

Precautions

General

If symptoms persist, consult a physician. Overdose may lead to nausea or vomiting (*7, 24*).

Carcinogenesis, mutagenesis, impairment of fertility

Intragastric administration of 1.6 ml/kg bw of a combination product containing a 40% ethanol extract of Radix Gentianae Luteae, chamomile and liquorice per day for 13 weeks produced no effects on reproduction, fertility or mating in female rats and rabbits (*35*).

The mutagenicity of a methanol extract of Radix Gentianae Luteae, and two isolated minor hydroxyxanthone constituents, gentisin and isogentisin, was assessed in vitro. The methanol extract was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA100 with metabolic activation with rat liver homogenate S9 enzyme mix. Gentisin and isogentisin, up to 50 µg/plate, were mutagenic after similar metabolic activation in *S. typhimurium* strains TA97, TA98, TA100 and TA2637 (*36–38*).

Pregnancy: teratogenic effects
Intragastric administration of 1.6 ml/kg bw of a combination product containing alcohol extracts of Radix Gentianae, chamomile and liquorice per day for 13 weeks had no teratogenic effects in rabbits (*35*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms

Dried roots and rhizomes; dried extracts of the roots and rhizomes for infusions, elixir, extracts, fluidextracts, glycerinated elixir and tinctures (*8, 23*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average adult daily dose: 0.1–2 g of the roots and rhizomes in 150 ml of water as an infusion, decoction or maceration, up to three times per day; fluidextract, 2–4 g; tincture (1 part roots and rhizomes:5 parts ethanol 45–70 % v/v) 1 ml three times per day; hydroethanolic extracts with an equivalent bitterness value (*7, 8, 11, 24*).

To stimulate the appetite, administer a single dose of a Radix Gentianae Luteae preparation one hour prior to meals (*11*); for dyspepsia, a single dose after a meal (*7, 24*).

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Radix Gentianae Scabrae

Definition
Radix Gentianae Scabrae consists of the dried roots and rhizomes of *Gentiana scabra* Bunge (Gentianaceae) (*1–4*).

Synonyms
Gentiana buergeri Miq., *G. fortunei* Hook. (*5*).

Selected vernacular names
Chinese gentian, dancao, Japanese gentian, kudancao, longdan, longdancao, tourindou (*1, 2, 4, 6, 7*).

Geographical distribution
Indigenous to the Korean peninsula and to China and Japan (*8, 9*).

Description
A perennial herb. Roots white, 10–15 cm long, with numerous short branches. Rhizomes rather short. Stems 20–100 cm long, with 10–20 pairs of leaves. Leaves lanceolate to narrowly deltoid-ovate, 4–8 cm long, 1–3 cm wide, gradually acuminate, three-nerved, green above, paler beneath, usually sessile, margin of upper leaves papillose. Flowers few to rather numerous, sessile, 4.5–6 cm long, purplish-blue; calyx tube 12–18 mm long, the lobes rather unequal, linear-lanceolate; corolla plaits deltoid, often toothed. Capsules stipitate, not exerted; seeds broadly lanceolate, short-caudate at both ends (*10, 11*).

Plant material of interest: dried roots and rhizomes
General appearance
Irregular, cylindrical, short yellowish-brown to greyish-brown rhizome with numerous slender roots. Roots 10–15 cm long, about 0.3 cm in diameter, with longitudinal, coarse wrinkles on the outer surface; flexible, fractured surface, smooth, yellow-brown. Rhizome about 2 cm long, 0.7 cm in diameter, with buds or short remains of stems at the top (*2*).

Organoleptic properties
Odour: characteristic; taste: bitter (*1–4*).

Microscopic characteristics
Root section shows epidermis, endodermis and a few layers of primary cortex; usually the outermost layers of the endodermis consisting of characteristic cells divided into a few daughter cells, often with collenchyma of one to two layers in contact with the inner side; secondary cortex having rents here and there, and irregularly scattered sieve tubes; vessels ranging rather radially in the xylem, and sieve tubes existing in the phloem. Root and rhizomes have distinct pith, rarely with sieve tubes, and parenchymatous cells containing needle, plate or rhombic crystals of calcium oxalate, and oil droplets. Starch grains mostly absent (*1, 2, 4*).

Powdered plant material
Fragments of parenchymatous cells containing oil droplets and minute needle crystals of calcium oxalate. Cells of exodermis spindle-shaped in surface view, each cell divided by transverse walls into several small rectangular cells. Cells of endodermis subrectangular in surface view, fairly large, periclinal walls showing minute transverse striations, each cell divided by longitudinal septa walls into several small palisade-like cells, longitudinal septa mostly beaded. Vessels mainly reticulate and scalariform, 20–30 μm but can be up to 45 μm in diameter (*2, 4*).

General identity tests
Macroscopic and microscopic examinations (*1–4*), microchemical tests (*1, 3*) and thin-layer chromatography (*2, 4*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Total ash
Not more than 7% (*1–4*).

Acid-insoluble ash
Not more than 3% (*1–3*).

Alcohol-soluble extractive
Not less than 30% (*3*).

Loss on drying
Not more than 8% (*3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

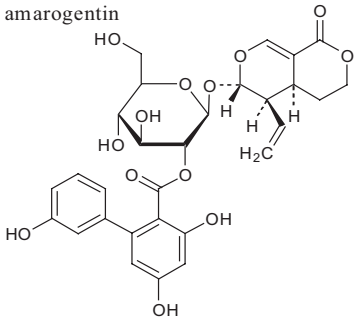
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and water-soluble extractive tests to be established in accordance with national requirements.

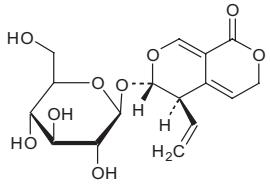
Chemical assays
Contains not less than 1.0% gentiopicroside determined by high-performance liquid chromatography (*4*).

Major chemical constituents
The major constituents are bitter secoiridoid monoterpenes including gentiopicroside (gentiopicrin; 0.5–10%), swertiamarin and sweroside. Xanthones, the alkaloid gentianine (0.05%) and gentianadine are other significant constituents. The bitter principle amarogentin found in *Gentiana lutea* is absent (*5, 7, 15–17*). Representative structures of the secoiridoid monoterpenes are presented below.

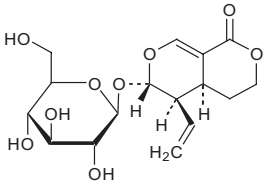
amarogentin



gentiopicroside



sweroside



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of liver disorders, cholecystitis and lack of appetite (*3, 6*).

Uses described in traditional medicine

Treatment of convulsions, eczema, fungal infections, hearing impairment, inflammation, leukorrhoea, otitis media, urinary tract infections, herpes zoster and pruritus vulvae (*3, 6, 7*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A 90% ethanol extract of the roots did not inhibit the growth of *Bacillus subtilis*, *Candida albicans, Escherichia coli, Staphylococcus aureus* or *Streptococcus faecalis* in vitro (*18*). An infusion of Radix Gentianae Scabrae had no antiviral activity in vitro when tested against herpes simplex virus 1, measles virus or poliovirus 1 (*19*).

Antihepatotoxic activity

Intraperitoneal administration of 1.0 g/kg body weight (bw) of a dried methanol extract of the roots and rhizomes, dissolved in normal saline, inhibited hepatotoxicity induced by carbon tetrachloride in rats but did not decrease the activity of alkaline phosphatase (*20*). Intraperitoneal administration of 1.0 g/kg bw of a dried methanol extract of the roots and rhizomes, dissolved in normal saline, to rats decreased increased glutamate-oxaloacetate transaminase activity induced by treatment with α-naphthylisothiocyanate and decreased plasma bilirubin concentrations, but did not decrease the activities of glutamate-pyruvate transaminase or lactate dehydrogenase (*20*). Intragastric administration of 670.0 mg/kg bw of a 1-butanol, chloroform or methanol extract of the roots and rhizomes prevented hepatotoxicity induced by carbon tetrachloride in mice (*21, 22*). The 1-butanol and chloroform extracts also inhibited the increased glutamate-pyruvate transaminase activity induced by carbon tetrachloride (*20*). Intraperitoneal administration of an aqueous or dried 50% methanol extract of the roots and rhizomes (dose not specified) prevented hepatotoxicity induced by carbon tetrachloride in mice (*23*). Intraperitoneal administration of 25.0–50.0 mg/kg bw of gentiopicroside

inhibited liver injury induced by D-galactosamine/lipopolysaccharide in mice (*24*). Intraperitoneal pretreatment of mice with 30.0–60.0 mg/kg bw of gentiopicroside per day for 5 days, suppressed the increased concentrations of serum hepatic aminotransferases induced by carbon tetrachloride (*25*).

Anti-inflammatory activity

Intraperitoneal administration of 90.0 mg/kg bw of gentianine to rats reduced swelling and inflammation of the ankle joint of the hind leg induced by formalin or egg white (*26, 27*).

Antispasmodic activity

A 95% ethanol extract of the roots and rhizomes, 200.0 µg/ml, did not inhibit barium- or histamine-induced smooth muscle contractions in guinea-pig ileum in vitro; however, an aqueous extract, 200.0 µg/ml, inhibited barium-induced contractions (*28*). The essential oil of Radix Gentianae Scabrae induced relaxation of smooth muscles in guinea-pig trachea and ileum in vitro, with median effective doses of 108.0 mg/l and 76.0 mg/l, respectively (*29*).

Central nervous system effects

Intraperitoneal administration of 250.0 mg/kg bw of a methanol or 75% methanol extract of the roots and rhizomes per day for 3 days to mice did not enhance the effects of barbiturates or increase hexobarbital-induced sleeping times (*30–32*). Intragastric administration of 670.0 mg/kg bw of a 1-butanol or chloroform extract of the roots did not potentiate the effects of barbiturates in mice (*20*). An ethanol extract of the roots and rhizomes (concentration not specified) inhibited the reuptake of serotonin in rat brainstem neurons in vitro (*33*). Intraperitoneal administration of 25.0–100.0 mg/kg bw of gentianine or gentianadine potentiated the anaesthetic effects of pentobarbital and chloral hydrate in mice (*6*). Intragastric administration of 200.0–400.0 mg/kg bw of gentianine or 700.0–1000.0 mg/kg bw of gentianidine resulted in sedation and reduced spontaneous activity in mice (*6*).

Choleretic activity

Intraduodenal administration of 50.0 g/kg bw of an aqueous extract of the roots and rhizomes to healthy rats or rats with hepatic injuries increased bile flow. A similar effect was observed in healthy dogs after intravenous administration of 4.5 g/kg bw of the extract (*6*). Intragastric administration of 1.8 g/kg bw of a dried methanol extract of the roots and rhizomes had choleretic effects in rats (*34*).

Toxicology
The oral median lethal doses (LD_{50}) of gentianine and gentianadine in mice were 400.0 mg/kg bw and 1250.0 mg/kg bw, respectively (*6, 35*). The subcutaneous LD_{50} of gentianine in mice was > 500.0 mg/kg bw, and the intravenous LD_{50} was 250.0–300.0 mg/kg bw (*6*). The intraperitoneal LD_{50} of a 90% ethanol extract of the roots and rhizomes in mice was 1.0 g/kg bw (*18*). 2-Hydroxy-3-methoxybenzoic acid glucose ester isolated from the roots and rhizomes was found to be a potent antagonist of platelet-activating factor in vitro (*36*).

Clinical pharmacology
No information available.

Adverse reactions
Radix Gentiana Scabrae may cause impairment of digestion and, occasionally, headaches, flushing of the face and vertigo when taken after a meal (*37*).

Contraindications
Owing to potential mutagenic effects (*38*), Radix Gentianae Scabrae should not be used during pregnancy or nursing or in children under the age of 12 years. Radix Gentianae Scabrae is contraindicated in stomach disorders and liver failure (*3*).

Warnings
Overdose may lead to nausea or vomiting (*3*).

Precautions
Carcinogenesis, mutagenesis, impairment of fertility
An aqueous extract of the roots and rhizomes, 40.0 mg/plate or 50.0 mg/disc, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*39, 40*). In another investigation, an aqueous or methanol extract of the roots and rhizomes, 100.0 mg/ml, was active in the *Salmonella*/microsome assay and the *Bacillus subtilis* recombination assay (*38*). However, intraperitoneal injection of an aqueous extract of the roots and rhizomes at doses 10–40 times those used in traditional medicine had no mutagenic effects in mice (*40*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects during pregnancy.

Dosage forms
Dried roots and rhizomes and dried extracts for infusions and decoction (*3, 4*). Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Average daily dose: roots and rhizomes 3–6 g per day as an infusion or decoction (*4*).

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Gummi Gugguli

Definition
Gummi Gugguli consists of the air-dried oleo-gum resin exudate from the stems and branches of *Commiphora mukul* (Hook. ex Stocks) Engl. (Burseraceae) (*1–4*).

Synonyms
Balsamodendron mukul Hook. ex Stocks, *B. roxburghii* Stocks non Arn., *Commiphora roxburghii* (Stocks) Engl., *C. wightii* (Arn.) Bhandari (*2, 5*).

Selected vernacular names
Aflatan, baijahundana, bdellium, boe-jahudan, devadhüpa, gogil, gugaru, guggal, guggul, guggula, guggulu, gukkal, gukkulu, hill mango, Indian bdellium, Indian myrrh tree, itinnil, kiluvai, kondamamidi, koushikaka, kungiliyam, maisatchi, moghl, moghl-arabi, moghl-azragh, moghl-makki, moql, moqle-azraqi, mugul, mukul myrrh tree, pura, ranghan (*5–12*).

Geographical distribution
Indigenous to Bangladesh, India and Pakistan (*6, 7, 11, 13*).

Description
Woody, bushy shrub 1–4 m high. Stems and branches thorny, covered with wax and ash-coloured bark that peels into thin rolls. Leaves small, alternate, simple or trifoliate. Flowers unisexual or bisexual with a fuzzy calyx and a brownish-red corolla. Fruits are ovoid drupes that turn red when ripe (*6, 7, 13–15*).

Plant material of interest: dried oleo-gum resin
General appearance
Vermicular or stalactitic pale yellow or brown pieces; slightly sticky to touch; viscid and golden when fresh. Makes a milky emulsion in hot water; burns readily (*2, 3, 6, 16–18*).

Organoleptic properties
Odour: characteristic aromatic, balsamic; taste: aromatic, bitter, acrid (*2*, *3*, *6*, *16*).

Microscopic characteristics
Not applicable.

Powdered plant material
Not applicable.

General identity tests
Macroscopic appearance (*2*, *3*, *6*, *16–18*), ultraviolet spectrophotometry of an ethanolic solution (*2*), and thin-layer chromatography (*2*, *19*), and high-performance liquid chromatography for the presence of guggulsterones (*2*, *20*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*21*).

Foreign organic matter
Not more than 4% (*3*, *4*).

Total ash
Not more than 5% (*3*, *4*).

Acid-insoluble ash
Not more than 1% (*3*, *4*).

Sulfated ash
Not more than 10% (*2*).

Water-soluble extractive
Not less than 53% (*3*, *4*).

Alcohol-soluble extractive
Not less than 35% (*2*).

Ethyl acetate-soluble extractive
Not less than 25% (*2*).

Moisture
Not more than 14% (*18*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*22*). For other pesticides, see the *European pharmacopoeia* (*22*), and the WHO guidelines on quality control methods for medicinal plants (*21*) and pesticide residues (*23*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*21*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*21*) for the analysis of radioactive isotopes.

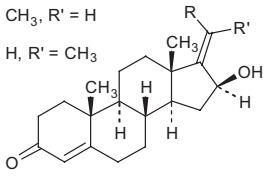
Other purity tests
Chemical tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 4.0% and not more than 6.0% of guggulsterones *Z* and *E* determined by high-performance liquid chromatography (*2*).

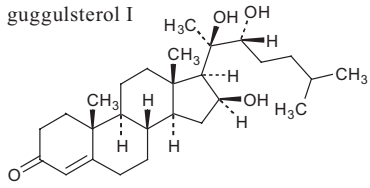
Major chemical constituents
A mixture of resins, essential oil (1.4–1.45%) (*13, 16*) and a water-soluble gum (made up of galactose, arabinose and 4-*O*-methylglucuronic acid (*5, 15*). The major constituents of the essential oil fraction of the oleo-gum resin are the monoterpene myrcene and the diterpene camphorene. The resinous fraction contains the diterpenes cembrene A and mukulol; the lignans sesamin and guggullignan-I and -II; and the sterols guggulsterol-I, -II, -III, -IV and -V, and *E*- and *Z*-guggulsterone (up to 15%) (*24*). *E*- and *Z*-guggulsterone are characteristic constituents that distinguish *Commiphora mukul* from other *Commiphora* species (*5, 11, 15, 17, 20, 25*). The structures of *E*- and *Z*-guggulsterones, guggulsterols-I, -II and -III, cembrene and mukulol are presented below.

Medicinal uses
Uses supported by clinical data
Treatment of hyperlipidaemia and hypercholesterolaemia (*1, 26–33*). Clinical investigations to assess the use of extracts of the oleo-gum

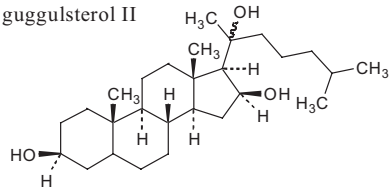
(*E*)-guggulsterone R = CH_3, R' = H
(*Z*)-guggulsterone R = H, R' = CH_3



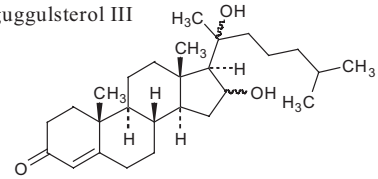
guggulsterol I



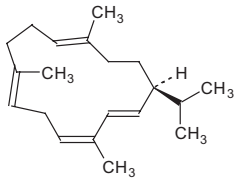
guggulsterol II



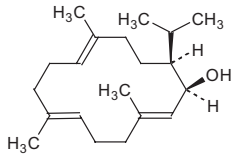
guggulsterol III



cembrene



mukulol



resin for the treatment of obesity were negative (*34, 35*) (see Clinical pharmacology).

Uses described in pharmacopoeias and well established documents

Treatment of atherosclerosis, rheumatic conditions, cough, sore throat and menopausal symptoms. As an emmenagogue (*3, 4, 8, 9, 16*).

Uses described in traditional medicine

Internally as an expectorant and for treatment of diarrhoea, fatigue, headache, jaundice and indigestion; topically for treatment of burns (*12, 16, 36–38*). Also as an insecticide and insect repellent (*9*).

Pharmacology

Experimental pharmacology

Anticoagulant activity

Intraperitoneal administration of 100.0 mg/kg body weight (bw) of an ethyl acetate extract of Gummi Gugguli to mice inhibited platelet aggregation (*39*). However, intraperitoneal administration of an aqueous extract of the oleo-gum resin to mice at the same dose was not active (*39*).

Antihypercholesterolaemic activity

Gummi Gugguli showed antihyperlipidaemic and antihypercholesterolaemic activities in animal models (*24, 40*). In chicks fed an atherosclerotic

diet, intragastric administration of a petroleum ether extract of the oleo-gum resin, 3.0 g/kg bw per day for 10 days or 2.0 g/kg bw per day for 30 days, significantly ($P < 0.001$) reduced serum cholesterol concentrations (*1*). In male chicks with estrogen-induced hyperlipidaemia, hypercholesterolaemia and weight gain, intragastric administration of 3 g/kg bw of a petroleum ether extract of the oleo-gum resin per day for 10 days reduced serum cholesterol concentrations and estradiol-induced weight gain (*1*). Histological examination showed an enhancement of the thyroid function in the treated animals, while suppression of thyroid function was observed in animals treated only with estradiol. In another study, intragastric administration of 5.0 mg/kg bw of a ketosteroid extract of the oleo-gum resin per day for one month to chicks fed an atherosclerotic diet and treated with carbimazole reduced serum cholesterol and triglyceride concentrations as compared with controls (*1*). In rats with dietary-induced hyperlipidaemia, administration of 10 mg/kg bw, 30 mg/kg bw or 100 mg/kg bw of an ethyl acetate fraction of the oleo-gum resin per day in the diet for 4 weeks significantly ($P < 0.001$) reduced total serum lipids and serum cholesterol, triglycerides and phospholipids (*9*). Similar hypolipidaemic effects of the oleo-gum resin have been observed in other animal species, such as dogs and monkeys (*41*).

The cholesterol-reducing activities of the oleo-gum resin are attributed to two closely related steroidal ketones, *trans*- and *cis*-guggulsterone (*E*- and *Z*-guggulsterone) (*20*). While the other chemical constituents do not have cholesterol-reducing activity individually, they act synergistically to enhance the overall antihypercholesterolaemic effects of the oleo-gum resin (*24*).

Anti-inflammatory activity

Intragastric administration of 500.0 mg/kg bw of an ethyl acetate fraction of the oleo-gum resin per day for a period of 5 months to rabbits decreased joint swelling induced by intra-articular injection of mycobacterial adjuvant (*42*). Intragastric administration of 400.0 mg/kg bw of an aqueous extract of the oleo-gum resin significantly ($P < 0.05$) reduced carrageenan-induced hind-paw oedema in rats by 59% (*43*). Administration of 400.0 mg/kg bw of a petroleum ether extract of the oleo-gum resin per day for 18 days to rats with arthritis induced by Freund's adjuvant significantly ($P < 0.05$) reduced the development of inflammation (*43*). Intraperitoneal administration of 200–400.0 mg/kg bw of a 100% ethanol extract of the oleo-gum resin reduced xylene-induced ear inflammation in mice by 50% (*44*). Intraperitoneal administration of 5.0 mg/kg bw of a steroid-containing fraction of a petroleum ether extract of the oleo-gum

resin to rats inhibited primary and secondary inflammation induced by Freund's adjuvant (*45*).

Antiobesity activity

Intragastric administration of 3.0 g/kg bw of the oleo-gum resin per day to rats and rabbits fed a high-fat and high-carbohydrate diet over a 4-month period reduced weight gain and the percentage of body fat (*1*). However, in rats fed a high-fat diet, treatment with 10.0 mg/kg bw, 30.0 mg/kg bw or 100.0 mg/kg bw of an ethyl acetate extract of the oleo-gum resin per day administered in the diet for 4 weeks did not reduce body weight as compared with controls (*9*).

Effects on thyroid function

Intragastric administration of a steroidal extract of 200.0 mg/kg bw of the oleo-gum resin per day for 15 days to mice induced triiodothyronine production and increased the triiodothyronine:thyroxine ratio (*46*). Intragastric administration of a ketosteroid isolated from a petroleum ether extract of 10.0 mg/kg bw of the oleo-gum resin per day for 6 days to rats significantly increased iodine uptake in the thyroid ($P < 0.05$) and enhanced the activities of thyroid peroxidase and protease ($P < 0.001$) (*40*).

Toxicology

Acute and chronic oral toxicity studies of an ethyl acetate extract of the oleo-gum resin were conducted in rats, mice and dogs (*47*). No mortality was observed in the 72 hours following administration of 5.0 mg/kg bw in all species. In dogs, no mortality was observed following oral administration of 1.0 g/kg bw per day over a period of 3 months. However, in rats, the mortality rate following administration of 250.0 mg/kg bw per day over the same period was 50%, compared with 20% in controls (*47*).

Clinical pharmacology

The effect of the oleo-gum resin was assessed in a parallel, placebo-controlled clinical trial in 40 patients with hyperlipidaemia: 20 patients received 4.5 g of the oleo-gum resin per day in two divided oral doses for 16 weeks; 20 controls received placebo administered at the same dose and in accordance with the same schedule. At the end of the 16-week treatment period, serum concentrations of cholesterol decreased by 21.75%; those of high-density lipids increased by 35.8% ($P < 0.01$) in the treated group as compared with controls. Serum triglyceride concentrations decreased by 27.1% in the treated group as compared with placebo control ($P < 0.01$) (*32*).

The hypolipidaemic effects of a standardized ethyl acetate extract of the oleo-gum resin containing approximately 4.0 g of *Z*- and *E*-gug-

gulsterones per 100.0 g of extract were compared with those of ethyl-*p*-chlorophenoxyisobutyrate (EPC) and a test substance (Ciba-13437-Su) in a randomized comparison trial in 44 patients with hyperlipidemia. Patients received 500.0 mg of oleo-gum resin extract twice per day, 500.0 mg of EPC three times per day, or 100.0 mg of the test substance three times per day for 6–36 weeks. Serum total lipids, cholesterol and triglycerides were measured before and after treatment. The oleo-gum resin extract significantly reduced total serum lipids by 34%, cholesterol by 27% and triglycerides by 29% ($P < 0.001$), and was as effective as or superior to the two other compounds tested (*26*).

A standardized ethyl acetate extract of the oleo-gum resin was compared with clofibrate in a long-term clinical trial. Of the 51 patients with hyperlipidaemia, 41 were treated with 1.5 g of the extract and 10 were treated with 2.0 g of clofibrate daily for a mean treatment period of 75 weeks. The extract significantly ($P < 0.001$) reduced serum cholesterol (26.2%) and triglycerides (36.5%). Clofibrate also significantly ($P < 0.001$) reduced total serum cholesterol (31.3%) and triglyceride concentrations (33.3%) (*28*).

In a phase I clinical trial to assess the safety of a standardized ethyl acetate extract of the oleo-gum resin, oral administration of 400.0 mg of the extract three times per day for 4 weeks to 21 hyperlipidaemic patients was safe and did not have any adverse effects on liver function, blood sugar, blood urea or haematological parameters (*30*). In a subsequent phase II clinical trial involving 19 patients with primary hyperlipidaemia (serum cholesterol > 250.0 mg/dl and serum triglycerides > 200.0 mg/dl), the same extract was administered orally, 500.0 mg three times per day for 12 weeks following 6 weeks of dietary control. Follow-up at 4-week intervals indicated that serum cholesterol and triglyceride concentrations were lowered in 15 patients (76.9%) after 4 weeks of treatment. The average decreases were 17.5% and 30.3%, respectively (*30*).

In a placebo-controlled trial, 120 obese patients with hyperlipidaemia received 2.0 g of the oleo-gum resin twice per day, 0.5 g of a petroleum ether fraction of the oleo-gum resin three times per day, a placebo daily or clofibrate daily for 21 days. The oleo-gum resin and clofibrate significantly decreased the mean serum cholesterol level after 10 days ($P < 0.01$ and $P < 0.1$, respectively). The petroleum ether fraction also significantly ($P < 0.05$) reduced serum cholesterol concentrations after 10 days of treatment as compared with placebo (*27, 29*).

Oral administration of 50.0 mg of an ethyl acetate extract of the oleo-gum resin or placebo capsules twice per day for 24 weeks as adjuncts to a fruit- and vegetable-enriched diet were compared for the management of

61 patients with hypercholesterolaemia in a randomized, double-blind study (*33*). The oleo-gum resin decreased the serum levels of total cholesterol (11.7%), low-density lipoprotein cholesterol (12.5%) and triglycerides (12.0%) in the treated group as compared with placebo; blood lipid peroxides, indicating oxidative stress also declined (33.3%) (*33*).

The effects of an ethyl acetate extract of the oleo-gum resin on serum cholesterol, fibrinolytic activity and platelet adhesive index were assessed in 20 healthy subjects and 20 subjects with cardiovascular disease. Both groups received 500.0 mg of the extract twice per day for 30 days. Serum fibrinolytic activity in the two groups increased by 22% and 19% in healthy volunteers and patients with cardiovascular disease, respectively, after 24 hours, and by 40% and 30% after 30 days; platelet adhesive index decreased by 19% and 16%. There was no decrease in serum cholesterol concentrations (*48*).

In a controlled clinical trial, 75 subjects were divided into three groups of 25 subjects, which received placebo, encapsulated oleo-gum resin (16.0 g) or a petroleum ether extract of the oleo-gum resin (dose equivalent to that of the oleo-gum resin) daily for 3 months. Serum cholesterol levels were significantly reduced in both treatment groups as compared with controls: by 24.2% ($P > 0.001$) in the oleo-gum resin group; and by 30.0% ($P > 0.001$) in the extract group (*1*).

In a double-blind, placebo-controlled clinical trial, 62 subjects, at least 10% overweight, received 1.5 g of an ethyl extract of the oleo-gum resin or matching placebo daily for 4 weeks. The extract significantly ($P < 0.01$) decreased (~10%) total serum cholesterol compared with placebo. However, there was no effect on body weight in either group (*34*).

In a randomized double-blind, placebo-controlled clinical trial, 84 obese subjects, at least 10% overweight, received 1.5 g of an ethyl acetate extract of the oleo-gum resin or matching placebo daily for 12 weeks. The extract significantly decreased (~20%) serum levels of total cholesterol ($P < 0.01$), total lipids ($P < 0.05$) and triglycerides ($P < 0.05$) compared with placebo. A slight, but significant reduction in body weight was observed at 4 weeks ($P < 0.05$) in the extract group, but at 12 weeks no significant effects on this parameter were observed (*35*).

Adverse reactions

In clinical trials, minor adverse effects such as mild diarrhoea and restlessness have been reported (*26, 28*). In one clinical trial of the oleo-gum resin, gastrointestinal upset was noted in 17.5% of patients (*27*). Topical application of a diluted (8%) aqueous solution of an essential oil obtained from the oleo-gum resin was non-irritating, non-sensitizing and non-

phototoxic (*1*). However, application of an extract (not further specified) to human skin caused contact dermatitis (*49–51*). In clinical trials, the oleo-gum resin and petroleum ether extracts of the oleo-gum resin were reported to shorten the menstrual cycle and increase menstrual flow (*1*).

Contraindications

Gummi Gugguli is used traditionally as an emmenagogue (*12*), and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, the oleo-gum resin should not be used during pregnancy.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the oleo-gum resin, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*52*). Intraperitoneal administration of an aqueous extract of the oleo-gum resin at a dose 10–40 times the normal therapeutic dose did not have mutagenic activity (*52*). A hot aqueous extract of the oleo-gum resin, 40.0 mg/plate, inhibited mutagenesis induced by aflatoxin B1 in *S. typhimurium* strains TA98 and TA100 (*53*).

Intragastric administration of the oleo-gum resin (dose not specified) reduced the weight of rat uterus, ovaries and cervix, with a concomitant increase in their glycogen and sialic acid concentrations, suggesting an antifertility effect (*54*).

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Powdered oleo-gum resin; petroleum ether or ethyl acetate extracts of the oleo-gum resin; other galenical preparations (*1, 26, 30, 32*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: oleo-gum resin 3–4.5 g in two or three divided doses (*30, 32*); petroleum ether extracts of the oleo-gum resin 500 mg two or three times (*26*).

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Radix Harpagophyti

Definition
Radix Harpagophyti consists of the dried, tuberous, secondary roots of *Harpagophytum procumbens* DC. ex Meiss. (Pedaliaceae) (*1, 2*).

Synonyms
Harpagophytum burcherllii Decne (*3*).

Selected vernacular names
Afrikanische Teufelskralle, beesdubbeltjie, devil's claw, duiwelsklou, grapple plant, grapple vine, harpagophytum, kanako, khams, khuripe, legatapitse, sengaparele, Teufelskralle, Trampelklette, wood spider xwate (*3–8*).

Geographical distribution
Indigenous to the Kalahari desert and savannas of Angola, Botswana, Namibia and South Africa, being found southwards from central Botswana (*6, 7, 9–11*).

Description
Prostrate perennial mat-forming herb, up to 1.5 m across. Tuber up to 6 cm in diameter, bark yellowish-brown, longitudinally striated. Leaves pinnately lobed and clothed with glandular hairs, the underside densely pubescent. Flowers bright red, solitary, rising abruptly from the leaf axils; corolla pentamerous, tubular, pink-purple, up to 7 cm long; androecium of four stamens with one staminodium. Fruits characteristically large, hooked, claw-like, tardily dehiscent two-locular capsules, flattened at right angles to the septum, the edges bearing two rows of woody arms up to 8 cm long with recurved spines (*6, 12, 13*).

Plant material of interest: dried, tuberous, secondary roots
General appearance
Irregular thick, fan-shaped or rounded slices or roughly crushed discs of tuber, 2–4 cm and sometimes up to 6 cm in diameter, 2–5 mm thick,

greyish-brown to dark brown. Darker outer surface traversed by tortuous longitudinal wrinkles. Paler cut surface shows a dark cambial zone and xylem bundles distinctly aligned in radial rows. Central cylinder shows fine concentric striations. Seen under a lens, the cut surface presents yellow to brownish-red granules, longitudinally wrinkled; transverse surface yellowish-brown to brown, central region raised, fracture short (*1, 2*).

Organoleptic properties
Odour: none; taste: bitter (*1, 2*).

Microscopic characteristics
Several rows of large, thin-walled cork cells frequently with yellowish-brown contents; parenchymatous cortex with very occasional sclereids with reddish-brown contents, xylem arranged in concentric rings; reticulately thickened vessels, some with rounded perforations in the end walls (tracheidal vessels); abundant lignified parenchymatous cells associated with the vessels and in the small central pith (*1*).

Powdered plant material
Brownish-yellow with fragments of cork layer consisting of yellowish-brown, thin-walled cells; fragments of cortical parenchyma consisting of large, thin-walled cells, sometimes containing reddish-brown granular inclusions and isolated yellow droplets; fragments of reticulately thickened vessels and tracheidal vessels with associated lignified parenchyma from the central cylinder; small needles and crystals of calcium oxalate present in the parenchyma. May show rectangular or polygonal pitted sclereids with dark reddish-brown contents. Parenchyma turns green when treated with a solution of phloroglucinol in hydrochloric acid (*2*).

General identity tests
Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of harpagoside (*1, 2*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter
Not more than 2% (*1, 2*).

Total ash
Not more than 8% (*2*).

Acid-insoluble ash
Not more than 5% (*1*).

Water-soluble extractive
Not less than 50% (*1*).

Loss on drying
Not more than 12% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

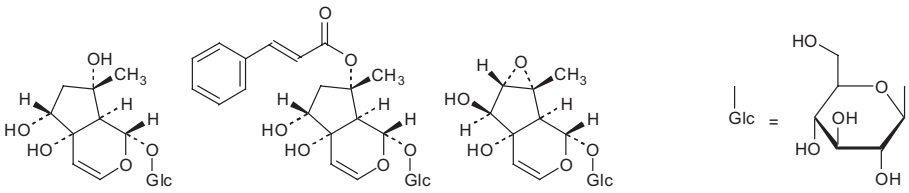
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 1.2% harpagoside as determined by high-performance liquid chromatography (*2*).

Major chemical constituents
The major active constituents are harpagoside and the related iridoid glycosides, harpagide and procumbide, which occur in lesser amounts. Total iridoid glycoside content 0.5–3.3% (*3, 7, 10, 11*). The structures of the major iridoid glycosides are presented below.

Medicinal uses
Uses supported by clinical data
Treatment of pain associated with rheumatic conditions (*17–24*).



Uses described in pharmacopoeias and well established documents
Treatment of loss of appetite and dyspeptic complaints; supportive treatment of degenerative rheumatism, painful arthrosis and tendonitis (*25*).

Uses described in traditional medicine
Treatment of allergies, boils, diabetes, liver disorders and sores (*8*).

Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity

A 60% ethanol extract of Radix Harpagophyti, 100.0 µg/ml, standardized to contain 2.9% harpagoside, inhibited the release of tumour necrosis factor-α (TNF-α) induced by the treatment of human monocytes with lipopolysaccharide (LPS) in vitro. However, treatment of the monocytes with harpagoside and harpagide, 10.0 µg/ml, isolated from the roots, had no effect on LPS-induced TNF-α release (*26*). Harpagoside, 10.0–100.0 µmol/l, reduced the synthesis of thromboxane B_2 in cells treated with calcium ionophore A23187 (*27*).

The results of studies assessing the anti-inflammatory activity of Radix Harpagophyti in animal models are conflicting. Intragastric administration of 20.0 mg/kg body weight (bw) of an aqueous or methanol extract of the root to rats inhibited oedema and inflammation in the granuloma pouch and carrageenan-induced footpad oedema tests (*28*). Intragastric administration of 20 mg/kg bw of a methanol extract of the root inhibited erythema induced by ultraviolet light in rats (*28*). Intragastric administration of 20.0 mg/kg bw of the same methanol extract to mice exhibited analgesic activity in the hot-plate test, but did not inhibit benzoquinone-induced writhing (*28*). Intraperitoneal pretreatment of rats with an aqueous extract of the roots reduced carrageenan-induced footpad oedema in a dose-dependent manner. Doses of 400 mg/kg bw and 1200 mg/kg bw reduced oedema by 43% and 64%, respectively, 3 hours after administration. The efficacy of the higher dose was similar to that of indometacin, 10 mg/kg bw (*29*). Intraperitoneal administration of 400.0 mg/kg bw of a

chloroform extract of the roots to mice with carrageenan-induced footpad oedema and inflammation reduced inflammation by 60.3% 5 hours after treatment (*30*).

Intraperitoneal administration of 200–400 mg/kg bw of an aqueous extract of the roots reduced carrageenan-induced footpad oedema in rats, but did not increase the reaction time of mice in the tail-flick hot-plate test. The anti-inflammatory activity of the highest dose was more efficient in rats than indometacin, 10.0 mg/kg bw. Treatment of the aqueous extract with 0.1 mol/l hydrochloric acid dramatically decreased the activity, suggesting that oral dosage forms should be enteric coated to protect the active principles from stomach acid. In the same study, harpagoside did not appear to be involved in the anti-inflammatory activity (*31*).

Intraperitoneal administration of 20.0 mg/kg bw of an aqueous extract of the roots to rats reduced formalin-induced arthritis. The effectiveness was comparable to that of phenylbutazone, 50.0 mg/kg bw. This study also demonstrated that intraperitoneal administration of 10–50 mg/kg bw of harpagoside to rats inhibits both formalin- and albumin-induced footpad oedema and formalin-induced arthritis (*32*).

Intragastric administration of 200.0 mg of an aqueous extract of the roots to rats inhibited formalin-induced footpad oedema (*33*). However, another study showed that intragastric administration of 1.0 g/kg bw of the powdered roots to rats did not inhibit carrageenan-induced footpad oedema or adjuvant-induced arthritis, as compared with other anti-inflammatory agents such as indometacin or acetylsalicyclic acid (*34*). Investigations of the antiphlogistic activity of harpagoside, harpagide and an aqueous extract of Radix Harpagophyti (doses not specified) indicated that all three substances had anti-inflammatory activity similar to that of phenylbutazone (*35*). In mice, intragastric administration of 100.0 mg/kg bw of harpagoside inhibited carrageenan-induced footpad oedema, and external application of 1.0 mg/ear reduced ear oedema induced by phorbol ester (*36*).

Intragastric administration of up to 100 times the recommended daily dose of powdered roots (6.0 g/kg bw) to rats did not reduce footpad oedema induced by carrageenan or *Mycobacterium butyricum*. Furthermore, the root preparation, 100.0 mg/ml, failed to inhibit prostaglandin synthase activity in vitro (*37*).

Antiarrhythmic activity

Intragastric administration of 100 mg/kg bw of an aqueous or methanol extract of the roots protected rats against ventricular arrhythmias induced by epinephrine-chloroform or calcium chloride (*38*). Intraperitoneal administration of 25 mg/kg bw of a methanol extract of the roots inhibited

cardiac arrhythmias induced by aconitine, epinephrine-chloroform or calcium chloride in fasted rats (*38*). Intragastric administration of 300–400 mg/kg bw of a methanol extract of the roots to normotensive rats reduced heart rate and arterial blood pressure (*38*). Other studies have demonstrated that lower doses of the extract have slight negative chronotropic and positive inotropic effects (*39*), whereas larger doses have a marked inotropic effect, with reductions in coronary blood flow. The inotropic effect is attributed to harpagide (*40*).

Clinical pharmacology

Antidyspeptic activity

A decoction of Radix Harpagophyti is one of the strongest bitter tonics known (*41*). Ingestion of a tea prepared from the root (dose not specified) over a period of several days led to an improvement in the symptoms of disorders of the upper part of the small intestine, which were accompanied by disturbances of choleresis and bile kinesis (*41*). It has been proposed that, because the root is very bitter, is a good stomachic and stimulates the appetite, it may also be useful for the treatment of dyspeptic complaints (*17, 42, 43*).

Anti-inflammatory and analgesic activity

A randomized double-blind comparison study, involving 46 patients with active osteoarthritis of the hip, assessed the effects of oral administration of 480 ng of an ethanol extract of the roots twice daily in the successive reduction of ibuprofen use for pain and the Western Ontario and McMaster Universities (WOMAC) arthrosis index. Patients received, in conjunction with the extract or placebo, 800.0 mg of ibuprofen daily for 8 weeks, then 400.0 mg daily for 8 weeks, then no ibuprofen. After 20 weeks of treatment, the WOMAC index decreased in the treatment group, with improvements in pain, stiffness and loss of function (*23*). In a randomized, double-blind clinical trial in 122 patients suffering from osteoarthritis of the knee and hip, the efficacy and tolerance of the roots and diacerein were compared. Patients received the roots as 6 capsules per day, each containing 435.0 mg of powdered roots or 100.0 mg of diacerein daily for 4 months. Assessments of pain and functional disability were made on a 10-cm horizontal visual analogue scale, and the severity of osteoarthritis was evaluated using the Lequesne functional index. There was a reduction in spontaneous pain and a progressive reduction in the Lequesne index in both groups. Fewer side-effects were observed in the group treated with the powdered roots (8.1%) than in the group receiving diacerein (26.7%) (*22*).

In a double-blind, placebo-controlled clinical trial, 50 patients with various arthroses were treated with 1200.0 mg of a hydroalcoholic extract of the roots, containing 1.5% iridoid glycosides, daily for 3-week courses. The severity of pain was assessed 10 days after completion of treatment. Each patient was given one to three courses of treatment. Compared with placebo, the extract produced a decrease in the severity of pain in individuals with a moderate pain level (*44*).

In an uncontrolled study involving 630 patients with arthrosis, 42–85% of the patients showed improvements after 6 months of daily oral treatment with 3.0–9.0 g of an aqueous extract of the roots containing 2.5% of iridoid glycosides (*45*). In an uncontrolled trial, the efficacy of an orally administered aqueous extract of the roots (as tablets) was assessed in 13 patients, 11 with arthritis and two with psoriatic arthropathy. Treatment of the patients for 6 weeks with 1.23 g daily did not reduce pain or inflammation in 12 patients, and one patient withdrew owing to side-effects (*46*). In an uncontrolled study, beneficial results were reported in 80% of 60 patients with chronic polyarthritis after treatment with subcutaneous lateral and medial injections of aqueous root extracts on both sides of the knee joint (*17*).

The efficacy of a standardized hydroalcoholic extract of the roots for the treatment of chronic back pain was assessed in a double-blind, randomized, placebo-controlled trial. The 197 patients were treated orally with 600.0 mg or 1200.0 mg of the extract (standardized to contain a total of 50–100 mg of harpagoside) or placebo daily for 4 weeks. A total of 183 patients completed the trial. Three, six and ten patients in the placebo, low-dose extract and high-dose extract groups, respectively, ($P = 0.027$) remained pain-free without the permitted pain medication (tramadol) for 5 days in the last week (*20*). A 4-week randomized double-blind, placebo-controlled clinical trial assessed the safety and efficacy of an ethanol extract of the roots in the treatment of acute attacks of pain in 118 patients with chronic back problems. Patients received two 400.0-mg tablets three times per day (equivalent to 6 g of roots containing 50.0 mg of harpagoside). Intake of a supplementary analgesic (tramadol) did not differ significantly between the placebo and the treatment group. However, further analysis revealed that nine out of 51 patients who received the extract were pain free at the end of the treatment period, compared to only one out of 54 in the placebo group (*18*). The efficacy of a dried ethanol extract of the roots was investigated in a 4-week, double-blind, placebo-controlled study in 118 patients with a history of chronic lower back pain. Patients were randomly assigned to receive two tablets of the extract or placebo three times per day. After 4 weeks of treatment, a reduction in the

Arhus low back pain index was observed in the treated patients compared with those receiving placebo (*19*). A randomized, placebo-controlled, double-blind study investigated the effects of an ethanol extract of the roots on sensory, motor and vascular mechanism of muscle pain in 65 patients with mild to moderate muscle tension or mild back, shoulder or neck pain. Patients received two doses of 480.0 mg of the extract or placebo daily for 4 weeks. At the end of the treatment period, a significant reduction in muscle pain as measured by a visual analogue scale ($P < 0.001$) was observed in the extract group. Muscle stiffness and ischaemia were also improved in this group, but no changes were found in antinociceptive muscle reflexes or surface electromyography (*24*).

Oral administration of powdered roots, four 500.0-mg capsules, standardized to contain 3% total iridoids, daily for 21 days to healthy volunteers did not statistically alter eicosanoid biosynthesis by the cyclooxygenase or 5-lipoxygenase pathways. The results indicated that in healthy humans Radix Hapagophyti did not inhibit arachidonic acid metabolism (*47*).

Adverse reactions

Mild and infrequent gastrointestinal symptoms were reported in clinical trials (*18, 20, 45*).

Contraindications

Radix Harpagophyti is contraindicated in gastric and duodenal ulcers, and cases of known hypersensitivity to the roots (*25*). Owing to a lack of safety data, Radix Harpagophyti should not be used during pregnancy and nursing.

Warnings

No information available.

Precautions

General

Patients with gallstones should consult a physician prior to using the roots (*25*).

Drug interactions

An extract of the roots did not inhibit the activity of cytochrome P450 isoform 3A4 in vitro, suggesting that Radix Harpagophyti would not interact with prescription drugs metabolized by this enzyme (*48*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Other precautions
No information available on precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic effects during pregnancy; or paediatric use.

Dosage forms
Dried roots for decoctions and teas; powdered roots or extract in capsules, tablets, tinctures and ointments (*6, 7*). Store in a well closed container, protected from light (*2*).

Posology
(Unless otherwise indicated)
Daily dose: for loss of appetite 1.5 g of the roots in a decoction, 3 ml of tincture (1:10, 25% ethanol) (*25*); for painful arthrosis or tendonitis 1.5–3 g of the roots in a decoction, three times, 1–3 g of the roots or equivalent aqueous or hydroalcoholic extracts (*41*).

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Rhizoma Hydrastis

Definition
Rhizoma Hydrastis consists of the dried rhizomes and roots of *Hydrastis canadensis* L. (Ranunculaceae) (*1–3*).

Synonyms
Hydrastis canadensis was formerly classified as a member of the family Berberidaceae.

Selected vernacular names
Eyebalm, golden seal, goldenseal, gorzknik kanadyjski, ground raspberry, hydraste, hydrastis, idraste, Indian dye, Indian paint, Indian turmeric, sceau d'or, warnera, wild curcuma, yellow puccoon (*4, 5*).

Geographical distribution
Indigenous to North America (*4, 6*).

Description
A perennial herb. Underground portion consists of a horizontal, branching rhizome bearing numerous long slender roots. Aerial part consists of a single radical leaf and a short stem 10–18 cm high, which bears near its summit two petiolate, palmate (five to seven lobes), serrate leaves and ends with a solitary greenish-white flower. Fruits are compound crimson berries somewhat similar to raspberries (*4*).

Plant material of interest: dried rhizomes and roots
General appearance
Rhizomes horizontal or oblique, subcylindrical, 1–6 cm long, 2–10 mm in diameter, occasionally with stem bases; numerous short upright branches terminating in cup-shaped scars and bearing encircling cataphyllary leaves. Externally, brown-greyish or yellowish-brown, deep longitudinal wrinkles, marked by numerous stem and bud-scale scars. From the lower

and lateral surfaces, arise many long, slender, brittle, curved, and wiry roots, frequently broken off to leave short protuberances or circular, yellow scars. Fracture short and resinous; fractured surface yellowish-orange at centre and greenish-yellow at margin with thick, dark yellow to yellowish-brown bark. Bright yellow, narrow xylem bundles separated by wide medullary rays; large pith. Roots numerous, filiform up to 35 mm long and 1 mm in diameter, curved or twisted. Fracture short and brittle, fractured surface yellowish-orange to greenish-yellow (*1, 3, 4*).

Organoleptic properties

Odour: faint, unpleasant; taste: bitter, persistent (*1, 4, 6*).

Microscopic characteristics

Rhizome cork yellowish-brown, polygonal cells with thin lignified walls; secondary cortex contains abundant thin-walled, polygonal to round or elongated, parenchymatous cells and some collenchyma, with abundant starch grains, simple or rarely compound with two to six components, spherical or ovoid with small, round or slit-like hilum. Parenchyma contains numerous masses of granular, orange-brown matter. Lignified tracheids present, usually small with slit-like pits, but occasionally large vessels with reticulate thickening. Root cork consists of a single layer of cells, irregularly elongated. Very occasional fragments of piliferous layer from young roots with root hairs; and a few thin-walled, lignified fibres associated with vessels present. Occasional fragments of epidermis of stem bases composed of cells with thick, lignified, beaded walls, slightly elongated in surface view (*1, 3, 4*).

Powdered plant material

Dark yellow to moderate greenish-yellow. Numerous spherical, simple starch grains, 2–15 µm in diameter, the larger grains exhibiting a central hilum; a few compound forms with two to six components. Fragments of starch-bearing parenchyma and fibrovascular tissue. Tracheal elements with simple and bordered pores, some with spiral thickenings and wood fibres, 200–300 µm long, thin-walled and with simple pores. A few fragments of cork tissue, the cells of which have reddish-brown walls. Calcium oxalate crystals absent (*3, 4*).

General identity tests

Macroscopic and microscopic examinations (*1, 3, 4*), and thin-layer chromatography (*1, 3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

Chemical

Not less than 2.0% hydrastine and not less than 2.5% berberine (*3*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 9% (*3*).

Acid-insoluble ash

Not more than 5% (*3*).

Water-soluble extractive

Not less than 14% (*1*).

Loss on drying

Not more than 12% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*8*). For other pesticides, see the *European pharmacopoeia* (*8*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*9*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*7*).

Other purity tests

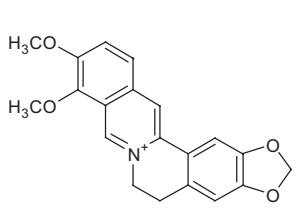
Sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

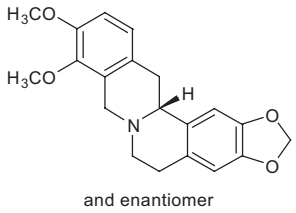
Contains not less than 2.0% hydrastine and not less than 2.5% berberine determined by high-performance liquid chromatography (*3*).

Major chemical constituents

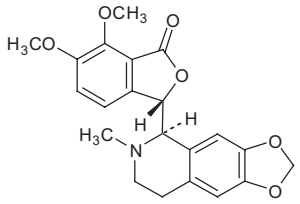
The major constituents are isoquinoline alkaloids (2.5–6.0%), principally hydrastine (1.5–5.0%), followed by berberine (0.5–4.5%), canadine (tetrahydroberberine, 0.5–1.0%), and lesser quantities of related alkaloids including canadaline, corypalmine, hydrastidine and jatrorrhizine (*5, 10–13*). The structures of hydrastine, berberine and canadine (a mixture of α-canadine (*R*-isomer) and β-canadine (*S*-isomer)) are presented below:



berberine



canadine



hydrastine

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Treatment of digestive complaints, such as dyspepsia, gastritis, feeling of distension and flatulence (*1*).

Uses described in traditional medicine

Treatment of cystitis, dysmenorrhoea, eczema, haemorrhoids, uterine haemorrhage, inflammation, kidney diseases, menorrhagia, nasal congestion, tinnitus and vaginitis. As a cholagogue, diuretic, emmenagogue, haemostat, laxative and tonic (*5*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A methanol extract of Rhizoma Hydrastis and berberine inhibited the growth of *Helicobacter pylori* (the bacterium associated with dyspepsia, gastritis and peptic ulcer disease) in vitro, median inhibitory concentration

range 0.625–40.00 µg/ml (*14, 15*). A 95% ethanol extract of the rhizomes, 1.0 mg/ml, inhibited the growth of *Staphylococcus aureus*, *Klebsiella pneumoniae, Mycobacterium smegmatis* and *Candida albicans* in vitro (*16*). Berberine was the active constituent of the extract, minimum inhibitory concentration 25.0–50.0 µg/ml against *Staphylococcus aureus* and *Mycobacterium smegmatis* (*16, 17*). Berberine inhibited the growth of *Bacillus subtilis* and *Salmonella enteritidis* in vitro at concentrations of 1.0 mg/ml and 0.5 mg/ml, respectively (*18*). Berberine, 150.0 µg/ml, also inhibited the growth of *Clostridium perfringens* in vitro and, at 1.0 mg/ml, significantly ($P < 0.001$) inhibited the growth of and induced morphological changes in *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis* (*19*).

Effects on smooth muscle

A 70% ethanol extract of the rhizomes inhibited carbachol-induced contractions of isolated guinea-pig trachea in vitro, median inhibitory dose 1.6 µg/ml (*20*). In rabbit bladder detrusor muscle strips, an ethanol extract of the rhizomes inhibited contractions induced by isoprenaline, median effective concentration 40 nmol/l (*21*). An alcohol extract of the rhizomes reduced contractions induced by serotonin, histamine and epinephrine in isolated rabbit aortas (*22*). Investigations using the major alkaloids from the rhizomes assessed the antispasmodic mechanism of action in isolated guinea-pig tracheas (*23*). The median effective concentrations of berberine, β-hydrastine, canadine and canadaline were 34.2 µg/ml, 72.8 µg/ml, 11.9 µg/ml and 2.4 µg/ml, respectively. Timolol pretreatments antagonized the effects of canadine and canadaline, but not berberine or β-hydrastine (*23*).

Berberine, 1 µmol/l, induced relaxation of norepinephrine-precontracted isolated rat aortas (*24*). Berberine, 10^{-5} mol/l, induced relaxation in isolated precontracted rat mesenteric arteries (*25, 26*). Berberine, 0.1–100.0 µmol/l, suppressed basal tone and induced a concentration-dependent relaxation of phenylephrine-precontracted rabbit corpus cavernosum (*27*). Intracavernosal injection of 5.0 mg/kg of berberine to anaesthetized rabbits increased intracavernosal pressure from 12.7 mmHg to 63.4 mmHg, duration of tumescence ranging from 11.5 to 43.7 minutes (*27*). A hydroalcoholic extract of the rhizomes or berberine inhibited norepinephrine- and phenylephrine-induced contractions in isolated rabbit prostate strips with ED_{50} values of 3.92 µmol/l and 2.45 µmol/l, respectively (*28*).

Immunological effects

Intragastric administration of an extract (type not specified) of the rhizomes, 6.6 g/l in drinking-water, to rats for 6 weeks increased production of antigen-specific immunoglobulin M (*29*). Intraperitoneal administra-

tion of 10.0 mg/kg body weight (bw) of berberine per day for 3 days to mice before the induction of tubulointerstitial nephritis significantly ($P = 0.001$) reduced pathological injury, improved renal function, and decreased the numbers of CD3+, CD4+ and CD8+ T-lymphocytes (*30*).

Toxicology

The oral median lethal dose of berberine in mice was 329.0 mg/kg bw (*31*). Oral administration of 2.75 g of berberine to dogs produced severe gastrointestinal irritation, profuse watery diarrhoea, salivation, muscular tremors and paralysis; respiration was not affected. Postmortem examination showed the intestines to be contracted, inflamed and empty or containing mucous and watery fluid. Oral administration of berberine sulfate, 25.0 mg/kg bw, induced central nervous system depression in dogs lasting 6–8 hours; 50.0 mg/kg bw caused salivation and sporadic emesis; 100.0 mg/kg bw induced persistent emesis and death of all animals 8–10 days later (*31*).

Uterine stimulant effects

Hot aqueous extracts of the rhizomes, 1:200 in the bath medium, stimulated contractions in isolated guinea-pig uteri (*32*). However, an alkaloid-enriched extract of the rhizomes did not stimulate contractions in isolated mouse uteri (*33*). A 70% ethanol extract of the rhizomes inhibited spontaneous and oxytocin- and serotonin-induced contractions in isolated rat uteri, median inhibitory concentrations 10.0–19.9 µg/ml (*20*).

Clinical pharmacology

No controlled clinical studies available for Radix Hydrastis. While berberine has been shown to be effective for the treatment of bacterially-induced diarrhoea (*34–40*), ocular trachoma (*41*) and cutaneous leishmaniasis (*42–44*), the data cannot generally be extrapolated to include extracts of the rhizomes.

Adverse reactions

No information available on adverse reactions to Radix Hydrastis. However, high doses of hydrastine are reported to cause exaggerated reflexes, convulsions, paralysis and death from respiratory failure (*45*).

Contraindications

Radix Hydrastis is contraindicated in cases of known allergy to the plant material.

Warnings

No information available.

Precautions

General

Use with caution in patients with high blood pressure, diabetes, glaucoma and a history of cardiovascular disease.

Drug interactions

An ethanol extract of the rhizomes inhibited the activity of cytochrome P450 (CYP3A4) in vitro, median inhibitory concentration <1% (*46*). Concomitant administration of Radix Hydrastis with drugs metabolized via cytochrome P450 may therefore affect the metabolism of such drugs (*46*).

Carcinogenesis, mutagenesis, impairment of fertility

The genotoxic effects of berberine in prokaryotic cells were assessed in the SOS-ChromoTest in *Saccharomyces cerevisiae* (*47*). No genotoxic activity with or without metabolic activation was observed, and no cytotoxic or mutagenic effects were seen under nongrowth conditions. However, in dividing cells, the alkaloid induced cytotoxic and cytostatic effects in proficient and repair-deficient *Saccharomyces cerevisiae*. In dividing cells, the induction of frameshift and mitochondrial mutations and crossing over showed that the compound is not a potent mutagen (*47*).

Pregnancy: non-teratogenic effects

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended during pregnancy.

Nursing mothers

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in nursing mothers.

Paediatric use

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in children.

Other precautions

No information available on precautions concerning drug and laboratory test interactions; or teratogenic effects during pregnancy.

Dosage forms

Dried rhizomes and roots, dried extracts, fluidextracts, and tinctures (*1, 11*). Store dried rhizomes and roots in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Daily dose: dried rhizomes and roots 0.5–1.0 g three times, or by decoction; liquid extract 1:1 in 60% ethanol, 0.3–1.0 ml three times; tincture 1:10 in 60% ethanol, 2–4 ml three times (*1*).

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Radix Ipecacuanhae

Definition

Radix Ipecacuanhae consists of the dried roots and rhizomes of *Cephaelis ipecacuanha* (Brot.) A. Rich., of *C. acuminata* (Benth.) Karst. (Rubiaceae), or of a mixture of both species (*1–9*).

Synonyms

Cephaelis ipecacuanha: Callicocca ipecacuanha Brot., *Cephaelis emetica* Pers., *Evea ipecacuanha* (Brot.) Standl., *Ipecacuanha officinalis* (Brot.) Farw., *Psychotria emetica* Vell., *P. ipecacuanha* (Brot.) Muell. Arg. (also Stokes), *Uragoga emetica* Baill., *U. ipecacuanha* (Willd.) Baill. (*3, 8, 10*).

Cephaelis acuminata: Psychotria acuminata Benth., *Uragoga acuminata* (Benth.) O. Kuntze, *U. granatensis* Baill. (*3, 10*).

Selected vernacular names

Ark ad dhahab, Brazilian ipecac (= *Cephaelis ipecacuanha* (Brot.) A. Rich.), Cartagena ipecac (= *Cephaelis acuminata* (Benth.) Karst.), Cartagena ipecacuanha, ipeca, ipecac, ipecacuanha, ipecacuana, jalab, Kopfbeere, matto grosso, mayasilotu, Nicaragua ipecac (= *Cephaelis acuminata* (Benth.) Karst.), poaia, raicilla, raizcilla, Rio ipecac (= *Cephaelis ipecacuanha* (Brot.) A. Rich.), togeun (*1, 3, 5, 10–13*).

Geographical distribution

Indigenous to Brazil and Central America (*3, 8, 14*).

Description

Cephaelis ipecacuanha: A low straggling shrub. Underground portion consists of a slender rhizome bearing annulated wiry roots and slender smooth roots. Rhizome arches upwards and becomes continuous with a short, green, aerial stem bearing a few opposite, petiolate, stipulate, entire, obovate leaves. Flowers small, white and capitate, occurring in the leaf

axils; corolla infundibuliform. Fruits are clusters of dark purple berries, each containing two plano-convex seeds (*15*).

Cephaelis acuminata: Resembles *Cephaelis ipecacuanha*, but has a root with less pronounced annulations (*15*).

Plant material of interest: dried roots and rhizomes

General appearance

Cephaelis ipecacuanha: Roots somewhat tortuous pieces, from dark reddish-brown to very dark brown, seldom more than 15 cm long or 6 mm thick, closely annulated externally, completely encircled by rounded ridges; fracture short in the bark and splintery in the wood. Transversely cut surface shows a wide greyish bark and a small uniformly dense wood. Rhizome in short lengths usually attached to roots, cylindrical, up to 2 mm in diameter, finely wrinkled longitudinally, with pith occupying approximately one-sixth of the diameter (*4, 5*).

Cephaelis acuminata: Roots generally resemble those of *Cephaelis ipecacuanha* but differ in the following particulars: often up to 9 mm thick; external surface greyish-brown or reddish-brown with transverse ridges, 0.5–1.0 mm wide, at intervals of usually 1–3 mm, extending about halfway round the circumference and fading at the extremities into the general surface level (*4, 5*).

Organoleptic properties

Odour: slight, irritating, sternutatory; taste: bitter, nauseous, unpleasant (*1–4, 6, 9*).

Microscopic characteristics

Cephaelis ipecacuanha: Root cork narrow, dark brown, formed of several layers of thin-walled cells, usually with brown granular contents; phelloderm cortex parenchymatous, containing numerous starch granules, and scattered idioblasts with bundles of calcium oxalate raphides; phloem very narrow with short wedges of sieve tissues, but no fibres or sclereids; xylem wholly lignified consisting of tracheids, with rounded ends and linear pits, narrow vessels with rounded lateral perforations near the ends, substitute fibres with oblique, slit-like pits containing starch grains, a few lignified fibres, and traversed by medullary rays, one or two cells wide, lignified, containing starch; primary xylem, three-arched at the centre. Rhizome cork has a narrow parenchymatous cortex; endodermis, pericycle with thick-walled, pitted and elongated rectangular sclereids; phloem with fibres; xylem radiating with fibres having linear pits and spiral

vessels in the protoxylem and pith with isodiametric, lignified, thin-walled cells. Starch granules, rarely simple, mostly compound with two to eight components; individual granules oval, rounded or muller-shaped, 4–10 µm but can be up to 15 µm in diameter (*1, 3, 4*).

Cephaelis acuminata: Similar to *C. ipecacuanha*, but starch granules are larger, up to 22 µm in diameter (*4*).

Powdered plant material

Cephaelis ipecacuanha: Greyish-brown to light brown; numerous fragments of thin-walled parenchymatous cells filled with starch granules, scattered cells with bundles of raphides of calcium oxalate; a few brown fragments of cork; a few fragments of wood showing tracheids, tracheidal-vessels of fibrous cells with starch granules; calcium oxalate raphides, 20–80 µm long scattered throughout the powder, sometimes in fragments; numerous starch granules, simple or mostly compound with two to eight components; individual granules oval, rounded or muller-shaped, up to 15 µm in diameter. A few vessels and sclereids, and occasional phloem fibres from the rhizome (*1, 3*).

Cephaelis acuminata: Similar to *Cephaelis ipecacuanha*, but starch grain up to 22 µm in diameter (*1, 3*).

General identity tests

Macroscopic and microscopic examinations (*1–6, 8, 9*), microchemical tests (*1–3, 6, 8, 9*), and thin-layer chromatography (*4, 5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Foreign organic matter

Not more than 2% (*5, 9*).

Total ash

Not more than 5% (*2, 5, 6*).

Acid-insoluble ash

Not more than 3% (*2, 4, 5, 6*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*17*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 2% of total alkaloids calculated as emetine, determined by titration (*1–5, 9*). Assay for emetine and cephaeline by column chromatography plus spectrophotometry (*9*). A high-performance liquid chromatography method is also available.

Major chemical constituents

The major active constituents are isoquinoline alkaloids (1.8–4.0%), with emetine and cephaeline accounting for up to 98% of the alkaloids present. Content in *Cephaelis ipecacuanha*: emetine 60–70%, cephaeline 30–40%; in *Cephaelis acuminata*: emetine 30–50%, cephaeline 50–70%. A 30-ml dose of ipecac syrup contains approximately 24 mg of emetine and 31 mg of cephaeline (*18*). Other alkaloids of note are psychotrine, *O*-methylpsychotrine and ipecoside (*10, 13, 14, 19*). Representative structures of the alkaloids are presented below.

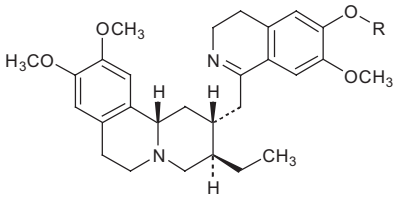
Medicinal uses

Uses supported by clinical data

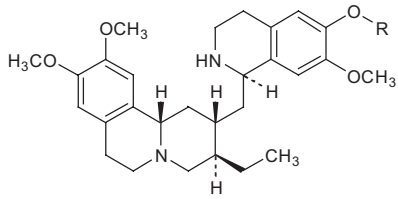
A syrup made from the roots is used as an emetic, to empty the stomach in cases of poison ingestion (*20*).

Uses described in pharmacopoeias and well established documents

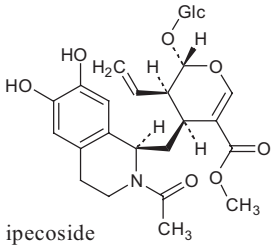
See Uses supported by clinical data (*20*).



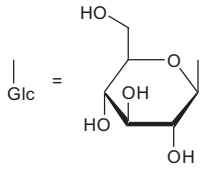
psychotrine R = H
O-methylpsychotrine R = CH_3



cephaeline R = H
emetine R = CH_3



ipecoside



β-D-glucopyranosyl

Uses described in traditional medicine

Treatment of parasites, the common cold and diarrhoea (*13*). Also to stimulate uterine contractions and induce abortion (*21*).

Pharmacology

Experimental pharmacology

In vivo studies

Experimental studies in animals are primarily limited to various investigations in dogs. In these studies most of the animals were not anaesthetized; however, some were premedicated to prevent spontaneous vomiting. The efficacy of a syrup made from Radix Ipecacuanhae to induce emesis was investigated in fasting dogs, pretreated by intramuscular or intravenous administration of 25.0 mg of chlorpromazine, 25.0 mg of promethazine or 37.5–50.0 mg of promethazine to prevent spontaneous vomiting. The pretreatments were administered 30 minutes prior to the oral administration of 500.0 mg/kg body weight (bw) of sodium salicylate in tablet form. The animals were then given 25.0 ml of a syrup made from the roots. When the syrup was administered orally within 30 minutes of the sodium salicylate dose, almost 50% of the salicylate was recovered. Administration after 30 minutes reduced recovery to 35.9% (*22*). In dogs, oral administration of 5 g of barium sulfate in suspension as a marker was followed by intragastric administration of 1.5 ml/kg bw of a syrup made from the roots at 0, 30 or 60 minutes. Mean time to emesis was 46 minutes, and recovery of the barium was 62%, 44% and 31%, respectively in the three groups (*23*). Fasting puppies were given two gelatin capsules of

barium sulfate (1.0 g) as a marker, followed after 20 minutes by intragastric administration of 15–30.0 ml of the syrup. Mean time to emesis was 29 minutes. Only three of the six dogs vomited and emesis resulted in a mean recovery of 19% (*24*). Paracetamol poisoning was induced in fasting dogs; drug emesis was 42.2% following intragastric administration of 20.0 ml of a syrup made from the roots given 10 minutes after the paracetamol dose (*25*).

Clinical pharmacology

In a randomized controlled crossover study, 10 fasting healthy volunteers received oral doses of paracetamol (3.0 g total dose), followed after 60 minutes by oral administration of 30.0 ml of a syrup prepared from the roots and 240.0 ml of water. Mean time to first emesis was 25.5 minutes. The 8-hour area under the curve for the paracetamol blood level in the syrup group was 21% lower than that for the control group (*26*).

Oral administration of 30.0 ml of a syrup prepared from the roots and 250.0 ml of water to 10 volunteers 60 minutes after the oral ingestion of 5.0 g of ampicillin prevented approximately 38% of the drug from being absorbed ($P < 0.01$). Mean time to emesis was 16 minutes (*27*).

In a randomized controlled crossover study, 10 of 12 volunteers were each given 24 acetylsalicylic acid tablets (81.0 mg/tablet) with 240.0 ml of water following a 12-hour fast. The two control subjects received no treatment. After 60 minutes, the volunteers were given 30.0 ml of a syrup prepared from the roots and 240.0 ml water; the dose was repeated in three subjects who did not vomit within 30 minutes of the initial dose. Time to emesis was approximately 30 minutes. Urine was collected for 48 hours. The proportion of ingested salicylate recovered in the urine was 96.3% for the control group and 70.2% for the treatment group ($P < 0.01$) (*28*).

In a randomized controlled crossover study 12 fasting adults were given 20 acetylsalicylic acid tablets (75.0 mg/tablet) with 200.0 ml of water followed by 30.0 ml of a syrup prepared from the roots 60 minutes later or no further treatment (control group). The mean percentage of ingested salicylate recovered in the urine was 60.3% for the control group and 55.6% for the treatment group ($P < 0.025$) (*29*).

In a controlled crossover study, oral administration of 1.0 g of paracetamol, 500.0 mg of tetracycline and 350.0 mg of a long-acting aminophylline preparation to six fasting adults was followed by oral administration of 20.0 ml of a syrup prepared from the roots and 300.0 ml of water administered either 5 minutes or 30 minutes later. Timed blood samples were collected over a 24-hour period. Mean time to onset of emesis was 14.3 minutes. For paracetamol, the mean peak serum concentra-

tion was reduced significantly ($P < 0.01$) to 4.4 mg/l after the administration of the syrup after 5 minutes compared with 14.9 mg/l in controls. Under these conditions the mean area under the curve was 35% of that in controls ($P < 0.01$). No statistically significant reduction in the mean peak serum concentration or mean area under the curve was observed when the syrup was given after 30 minutes. For tetracycline, the mean peak serum concentration and area under the curve were reduced significantly ($P < 0.01$) in both the 5- and 30-minute treatment groups. For aminophylline, the mean peak serum concentration was only reduced significantly ($P < 0.05$) in the 5-minute group (*30*).

In a randomized, controlled crossover trial, oral administration of 20.0 mg of metoclopramide to seven fasted adults was followed 60 minutes later by oral administration of 400.0 mg of cimetidine and 10.0 mg of pindolol, and after a further 5 minutes by 400.0 ml of water or 20.0 ml of a syrup prepared from Radix Ipecacuanhae and 400.0 ml of water. Six of the seven subjects vomited, with a mean time delay of 17 minutes. The syrup reduced the absorption of both cimetidine (25% of that in controls) and pindolol (40% of that in controls) as measured by mean peak serum concentrations (*31*).

In three investigations, markers were administered to emergency department patients presenting with potentially toxic ingestions, and recovery of the marker after syrup-induced emesis was measured. In one study, 14 children received an oral dose of 1.0 g of magnesium hydroxide prior to oral administration of 20.0 ml of a syrup prepared from the roots. Mean time to emesis was 15 minutes (range 5–41 minutes) and mean recovery of magnesium hydroxide was 28% (*32*). In a similar study, 100 mg of liquid thiamine mixed with 30 ml of a syrup prepared from the roots was administered to 51 subjects (*33*). Mean time to emesis was 21 minutes and mean recovery of thiamine was 50%. In a randomized, controlled, single-blind study, barium-impregnated 3-mm polythene pellets were administered with water and 30.0 ml of a syrup prepared from the roots to 20 patients. Time to emesis was 5–20 minutes. Abdominal X-rays were performed 15–80 minutes after ingestion of the pellets. In the syrup group, 39.3% of the ingested pellets had moved into the small bowel compared with 16.3% in the control group (*34*).

In a controlled, randomized prospective study, 592 acute oral drug overdose patients were evaluated to determine whether a syrup prepared from Radix Ipecacuanhae and activated charcoal or lavage and activated charcoal were superior to activated charcoal alone. The induction of emesis by the syrup before administration of activated charcoal and a cathartic ($n = 214$) did not significantly alter the clinical outcome of patients who were awake and alert on presentation compared with those who re-

ceived activated charcoal and a cathartic without the syrup ($n = 262$). The investigators concluded that induction of emesis in acutely poisoned patients who were alert and awake was of no benefit, even when performed less than 60 minutes after a toxic ingestion (*35*).

A prospective study was conducted to assess the effect of gastric emptying and activated charcoal upon clinical outcome in acutely self-poisoned patients. Presumed overdose patients ($n = 808$) were treated using an alternate-day protocol based on a 10-question cognitive function examination and presenting vital-sign parameters. Asymptomatic patients ($n = 451$) did not undergo gastric emptying. Activated charcoal was administered to asymptomatic patients only on even days. Gastric emptying in the remaining symptomatic patients ($n = 357$) was performed only on even days. On emptying days, alert patients had ipecac-induced emesis while obtunded patients underwent gastric lavage. Activated charcoal therapy followed gastric emptying. On non-emptying days, symptomatic patients were treated only with activated charcoal. No clinical deterioration occurred in the asymptomatic patients treated without gastric emptying. Use of activated charcoal did not alter outcome measures in asymptomatic patients. Gastric emptying procedures in symptomatic patients did not significantly alter the duration of stay in the emergency department, mean duration of intubation, or mean duration of stay in the intensive care unit. Gastric lavage was associated with a higher prevalence of medical intensive care unit admissions ($P = 0.0001$) and aspiration pneumonia ($P = 0.0001$). The data support the management of selected acute overdose patients without gastric emptying and fail to show a benefit from treatment with activated charcoal in asymptomatic overdose patients (*36*).

A prospective, randomized, unblinded, controlled trial was conducted to determine the effect of a syrup of the roots on the time to administration and duration of retention of activated charcoal, and on total duration of emergency department stay. The study involved 70 children less than 6 years old, who presented with mild–moderate acute oral poison ingestions. The children were divided into two groups, group 1 received the syrup before activated charcoal and group 2 received only activated charcoal. Duration from arrival to administration of activated charcoal was significantly longer in group 1 (2.6 h compared with 0.9 h, $P < 0.0001$) and group 1 children were significantly more likely to vomit activated charcoal (18 of 32 compared with 6 of 38, $P < 0.001$). Patients receiving the syrup who were subsequently discharged spent significantly more time in the emergency department than those receiving only activated charcoal (4.1 ± 0.2 h compared with 3.4 ± 0.2 h, $P < 0.05$). It was concluded that administration of the syrup delays the administration of activated charcoal, hinders its retention, and

prolongs the emergency department stay in paediatric ingestion patients (*37*). In a prospective randomized controlled trial, 876 patients were assessed on presentation to an emergency room after ingestion of a toxic substance. On odd-numbered days, the patients received 30–50 ml of syrup prepared from the roots followed by 200 ml of water, or gastric lavage followed by activated charcoal. On even-numbered days, no gastric emptying was performed and patients received 50 g of activated charcoal alone. No significant differences between the treatments were observed; syrup plus activated charcoal was not superior to activated charcoal alone (*38*).

A comparison study assessed the difference between early and late administration of ipecac syrup on paracetamol plasma concentrations. A total of 50 children under the age of 5 years with accidental ingestion of 150.0 mg/kg bw of paracetamol received ipecac syrup within 4 hours of ingestion: 23 received ipecac at home (mean time to administration 26 minutes after paracetamol ingestion) and had measured plasma paracetamol concentrations of 23.0 mg/l; 27 children received ipecac syrup elsewhere (i.e. not at home; mean time to administration, 83 min) and had measured plasma paracetamol concentrations of 44.0 mg/l. The investigators concluded that the shorter the time between ingestion of paracetamol and the administration of ipecac, the more effective ipecac was in reducing plasma paracetamol concentrations (*39*).

The rates of absorption and elimination of emetine and cephaeline from a syrup prepared from the roots were investigated in 10 healthy adults. Volunteers received an oral dose of 30 ml of the syrup and urine and blood samples were collected up to 180 minutes following ingestion. In all subjects emetine and cephaeline were detected in the blood 5–10 minutes after dosing, with maximum concentrations observed after 20 minutes. The mean areas under the curve were similar for both compounds. Less than 0.15% of the administered emetine and cephaeline doses was recovered in the urine at 3 hours. There was no relation between peak vomiting episodes and blood levels of emetine and cephaeline. At 3 hours neither alkaloid was detectable in the blood (*40*).

The roots act as an emetic because of their local irritant effect on the digestive tract and its effect on the chemoreceptor trigger zone in the area postrema of the medulla (*41*). Charcoal should not be administered with syrup prepared from the roots, because charcoal can absorb the syrup and reduce the emetic effect.

Adverse reactions

Large doses of Radix Ipecacuanhae have an irritant effect on the gastrointestinal tract, and may induce persistent bloody vomiting or diarrhoea

(*20*). Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which may occur if vomiting is not induced, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, in combination with dehydration, may cause vasomotor collapse followed by death. Chronic abuse of the roots to induce vomiting in eating disorders has been implicated in the diagnosis of cardiotoxicity and myopathy due to the accumulation of emetine (*20*). Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations may be observed (*20*). Cardiovascular toxicity, manifesting as muscle weakness, hypotension, palpitations and arrhythmias, may occur (*42, 43*). Death was reported for one subject who had ingested 90–120 ml of a syrup prepared from the roots per day for 3 months (*44*).

Prolonged vomiting has been reported in 17% of patients given the roots for the treatment of poisoning, which may lead to gastric rupture, Mallory-Weiss lesions of the oesophagogastric junction, cerebrovascular events, pneumomediastinum and pneumoperitoneum (*45*).

Allergy to the roots was reported after inhalation of powdered roots, characterized by rhinitis, conjunctivitis and chest tightness (*46*).

There have been a number of deaths reported in small children due to an overdose owing to the substitution of 10.0–60.0 ml of a fluidextract of the roots for a syrup prepared from the roots (*18, 47, 48*). It is believed that the fluidextract was mistaken for the syrup. The fluidextract is 14 times more potent than the syrup (*20*).

Other adverse reactions to the roots include severe diarrhoea, nausea and abdominal cramps (*49*).

Contraindications

While emesis is usually indicated after poisoning resulting from oral ingestion of most chemicals, emesis induced by Radix Ipecacuanhae is contraindicated in the following specific situations: following ingestion of a corrosive poison, such as strong acid or alkali; when airway-protective reflexes are compromised, for example in patients who are comatose or in a state of stupor or delirium; following ingestion of a central nervous system stimulant, when vomiting may induce convulsions; in cases of strychnine poisoning; or following ingestion of a petroleum distillate (*18, 41*). Radix Ipecacuanhae has been used as an abortifacient in traditional medicine and its use is therefore contraindicated during pregnancy. See also Warnings, and Precautions.

Warnings

Numerous deaths have occurred owing to the administration of a fluidextract of Radix Ipecacuanhae instead of a syrup prepared from the roots. The fluidextract is 14 times stronger than the syrup and should never be administered as a substitute for the syrup.

Precautions

General

Radix Ipecacuanhae should not be used as an emetic in patients whose condition increases the risk of aspiration or in patients who have taken substances that are corrosive or petroleum products that may be dangerous if aspirated (*20*). The roots should not be given to patients in shock, at risk of seizure, or with cardiovascular disorders (*20*).

Drug interactions

The emetic action of the roots may be delayed or diminished if given with or after charcoal. Concomitant administration of milk was believed to reduce the efficiency of emesis induced by the roots. However, no significant differences in the time to onset of vomiting, the duration of vomiting, or the number of episodes were observed in 250 children who were given a syrup prepared from the roots with milk compared with 250 children given the syrup with clear fluids (*50*).

Decreases in the absorption of paracetamol, tetracycline and aminophylline were observed after concomitant administration of 20.0 ml of an aqueous extract of the roots (*30, 51*).

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the roots, 50.0 µg/ml, was not mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 (*52*). The mutagenicity of a fluidextract of the roots was evaluated in the *Salmonella*/microsome assay, the chromosomal aberration test in cultured Chinese hamster lung cells and the mouse bone marrow micronucleus test (oral administration). No mutagenic effects were observed (*53*).

Pregnancy: non-teratogenic effects

See Contraindications.

Paediatric use

Do not exceed recommended doses. Do not give the fluidextract to children. For children up to 6 months of age, the syrup should only be administered under the supervision of a physician (*18*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic effects during pregnancy; or nursing mothers.

Dosage forms

Dried roots and rhizomes, liquid extracts, fluidextract, syrup and tincture (*20*). Dried roots and rhizomes should be stored in a tightly sealed container, protected from light (*20*).

Posology

(Unless otherwise indicated)

As an emetic in cases of poisoning other than corrosive or petroleum-based products. Doses should be followed by ingestion of copious volumes of water. Doses may be repeated once, 20–30 minutes after the initial administration, if emesis has not occurred (*20*). Adults: Ipecac Syrup, 15–30 ml (21–42 mg total alkaloids). Children: 6 months–1 year, 7–14 mg of total alkaloids (5–10 ml) of Ipecac Syrup; older children, 21 mg of total alkaloids represented in 15 ml Ipecac Syrup (*9*).

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Aetheroleum Lavandulae

Definition

Aetheroleum Lavandulae consists of the essential oil obtained by steam distillation from the fresh flowering tops of *Lavandula angustifolia* Mill. or of *L. intermedia* Loisel (Lamiaceae) (*1–4*).

Synonyms

Lavandula officinalis Chaix, *L. spica* Loisel., *L. vera* DC., *L. vulgaris* Lam. (*5–8*). Lamiaceae are also known as Labiatae. In most formularies and older reference books, *Lavandula officinalis* Chaix is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Lavendula angustifolia* Mill. is the legitimate name for the species (*8, 9*).

Selected vernacular names

Al birri, alhucema, arva neh, aspic, broad-leaved lavenda, common lavender, Echter Lavendel, English lavender, espi, espic, espliego común, firigla, frigous, garden lavendar, grando, hanan, hanene, hzama, khazama, khirii, khouzamaa, khouzami, khuzama, khuzama fassiya, khuzama zerqua, Kleiner Speik, Lavanda, lavande, lavande femelle, lavande véritable, lavando, lavandula vraie, Lavendel, lavender, lawanda, lófinda, ostoghodous, postokhodous, spigandos, true lavender (*6, 8–14*).

Geographical distribution

Indigenous to the northern Mediterranean region. Cultivated in southern Europe, and in Bulgaria, Russian Federation, United States of America, and the former Yugoslavia (*8, 15*).

Description

An aromatic shrub, 1–2 m high. Branches grey-brown to dark brown with long flowering and short leafy shoots, bark longitudinally peeling. Leaves clustered on leafy shoots, widely spaced on flowering shoots; petiole very short; blade linear-lanceolate to linear, 17 mm long, 2 mm wide

on leafy shoots, 2–6 cm long, 3–6 mm wide on flowering shoots; grey stellate tomentose, base attenuate, margin entire, revolute, apex obtuse. Inflorescence a crowded, interrupted or nearly continuous spike, 2–8 cm long; verticillasters numerous, with 6–10 flowers, upper ones densely crowded; peduncle about three times longer than the spike; bracts papery, rhombic-ovate, 3–8 mm long, rust coloured when dry; bracteoles absent or up to 2.5 mm long, pedicel 1.0–1.5 mm long; calyx 4–7 mm long, densely grey stellate tomentose outside, with 13 longitudinal ribs, upper lip entire, appendage obcordate, lower lip four-toothed; corolla 10–12 mm long, blue, base subglabrous, throat and limb glandular hairy, upper lips straight, lower lips spreading. Nutlets narrowly cylindrical (*8*).

Plant material of interest: essential oil

General appearance

A clear colourless or pale yellow liquid, miscible with 90% alcohol, ether and fatty oils (*1–4*).

Organoleptic properties

Odour: characteristic, fragrant, aromatic; taste: aromatic, slightly bitter (*1, 3*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Macroscopic examinations (*1, 3, 4*); refractive index, specific gravity and optical rotation measurements (*2*); thin-layer chromatography for the presence of linalyl acetate and linalool (*4*), and gas chromatography (*4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Chemical

Relative density 0.878–0.892 (*4*). Refractive index 1.455–1.466 (*4*). Optical rotation -12.5–7° (*4*). Acid value not more than 1.0 (*4*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Other purity tests

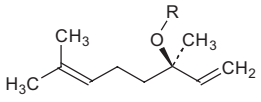
Tests for foreign organic matter, total ash and acid-insoluble ash not applicable. Tests for water-soluble extractive and acid-soluble extractive to be established in accordance with national requirements.

Chemical assays

Official analysis by gas chromatography shows the following composition: limonene, cineole, 3-octanone, camphor, linalool, linalyl acetate, terpinen-4-ol, lavandulyl acetate, lavandulol, α-terpineol (*4*).

Major chemical constituents

Contains: linalyl acetate (25–46%), linalool (20–45%), terpinen-4-ol (1.2–6.0%), lavendulyl acetate (> 1.0%), 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol) (< 2.5%), 3-octanone (< 2.5%), camphor (< 1.2%), limonene (< 1.0%), and α-terpineol (< 2.0%) (*4*). The structures of linalyl acetate and linalool are presented below.



and enantiomer

linalool R = H

linalyl acetate R = CO-CH_3

Medicinal uses

Uses supported by clinical data

Inhalation therapy for symptomatic treatment of anxiety, restlessness and to induce relaxation (*19–22*). Externally in balneotherapy for the treatment of circulation disorders (*23*).

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of insomnia, and as a carminative for the treatment of gastrointestinal disorders of nervous origin (*15, 24*).

Uses described in traditional medicine

Orally as a cholagogue, diuretic and emmenagogue; externally for the treatment of burns, diarrhoea, headaches, sore throats and wounds (*15*).

Pharmacology

Experimental pharmacology

Anaesthetic activity

In vitro, the essential oil, linalyl acetate and linalool, 0.01–10.0 µg/ml in the bath medium, reduced electrically-evoked contractions of a rat phrenic-hemidiaphragm (*25*). In the rabbit conjunctiva test in vivo, administration of an aqueous solution of the essential oil, linalyl acetate or linalool, 30.0–2500.0 µg/ml, into the conjunctival sac increased the number of stimuli needed to provoke the reflex (*25*).

Anticonvulsant and sedative activities

Intraperitoneal administration of 2.5 g/kg body weight (bw) of linalool to rodents protected against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*26, 27*). In mice, intraperitoneal administration of 2.5 g/kg bw of linalool interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*28*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes, suggesting interference of glutamatergic transmission. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool reduced potassium-stimulated glutamate release (*29*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity

The effect of Aetheroleum Lavandulae on immediate-type allergic reactions was investigated in vitro and in vivo. External and intradermal administration of aqueous dilutions of the essential oil, 1:500, 1:100, 1:10, 1:1 and 1:0, to mice inhibited mast cell-dependent ear oedema induced by compound 48/80 (*30*). Administration of the essential oil (same dose range) to rats inhibited passive cutaneous anaphylaxis induced by anti-dinitrophenyl (DNP) IgE, compound 48/80-induced histamine release and anti-DNP IgE-induced tumour necrosis factor-α secretion from peritoneal mast cells (*30*). Inhalation of 0.3 ml of the essential oil inhibited

thromboxane B_2 release induced by arachidonic acid in mice, suggesting an anti-inflammatory effect (*31*).

Antimicrobial and acaricidal activities
The undiluted essential oil inhibited the growth of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pneumoniae* in vitro (*32, 33*). The undiluted essential oil, 10.0 µl/disc, inhibited the growth of *Mycobacterium chelonae, M. fortuitum*, *M. kansasii*, *M. marinum* and *M. scrofulaceum* (*34*). The undiluted essential oil inhibited the growth of filamentous fungi in vitro (*35*). The essential oil, linalool, linalyl acetate and camphor had miticidal activity against *Psoroptes cuniculi* in rabbits (*36*).

Antispasmodic activity
Addition of the essential oil to the bath medium, 0.02 mg/ml and 0.2 mg/ml, reduced the twitching response and relaxed the muscle tone of rat phrenic nerve diaphragm preparations in vitro (*37*). The antispasmodic activity of the essential oil and linalool was mediated through the cyclic adenosine monophosphate signal transduction system, determined using a guinea-pig ileum smooth muscle preparation (*38*).

Central nervous system depressant effects
Inhalation of the essential oil (dose not specified) by mice reduced caffeine-induced hyperactivity, which was correlated with linalool serum levels (*39*). Intragastric administration of the essential oil (dose not specified) to rats produced anxiolytic effects and prolonged pentobarbital sleeping time (*40*).

Intragastric administration of 1.6 g/kg bw of the essential oil increased the lever-pressing response rate during the alarm phase of the Geller-type conflict test in animals, suggesting that the oil had an anticonflict effect similar to that of diazepam (*41*). Intragastric administration of 25.0 ml/kg bw of the essential oil, diluted 60 times in olive oil, prolonged pentobarbital sleeping times in mice (*42*). Inhalation of 0.3 ml of the essential oil inhibited strychnine-induced convulsions in mice (*31*).

Clinical pharmacology

Anxiolytic activity
In a comparison clinical trial without placebo, 40 healthy volunteers received aromatherapy (inhalation) with Aetheroleum Lavandulae or essential oil of rosemary (*Rosmarinus officinalis*) and were then asked to perform some simple mathematical computations. In the group treated with Aetheroleum Lavandulae, the electroencephalogram showed an increase in beta power, suggesting increased drowsiness. The subjects treated with this

oil also reported feeling less depressed and more relaxed, and performed the mathematical computation more accurately after the therapy (*20*).

In an uncontrolled trial in 13 healthy volunteers, inhalation of Aetheroleum Lavandulae significantly ($P < 0.001$) decreased alpha-1 frequencies (8–10 Hertz) shortly after inhalation, and the subjects reported feeling "comfortable" in a subjective evaluation of the treatment (*22*).

In a randomized study involving 122 patients admitted to a general intensive care unit, patients received either massage, aromatherapy with the oil (1% essential oil in grapeseed oil; 1–3 treatments over a 5-day period) or a period of rest to assess the efficacy of these factors on the stress response and anxiety. No difference between the three therapies was observed for the stress response. However, patients treated with the oil aromatherapy reported improvements in mood and a reduction of anxiety (*19*).

In 14 patients on chronic haemodialysis, inhalation of the essential oil over a one-week period decreased the mean score in the Hamilton anxiety rating scale compared with controls undergoing inhalation of odourless substances (*21*).

Analgesic activity

In a preliminary clinical trial without controls, addition of six drops of the essential oil to bath water daily for 10 days following childbirth did not reduce the incidence of perineal discomfort except for the period between days 3 and 5 postpartum (*43*). In a single-blind randomized clinical trial in 635 postpartum women, subjects were given pure Aetheroleum Lavandulae, synthetic lavender oil or an inert oil to use as a bath additive for 10 days postpartum. No difference between the therapies in the reduction of perineal discomfort was observed (*44*).

Cardiovascular effects

In a randomized crossover controlled study, healthy volunteers (number not specified) sat with their feet soaking in hot water for 10 minutes with or without the addition of the oil. Electrocardiogram, fingertip blood flow and respiration rate measurements indicated that treatment with the oil increased parasympathetic nerve activity and increased blood flow but had no effects on heart or respiratory rates (*23*).

Adverse reactions

Allergic contact dermatitis has been reported in patients previously exposed to the essential oil (*45–49*).

Contraindications

Aetheroleum Lavandulae is contraindicated in cases of known allergy to the plant material. Owing to its traditional use as an emmenagogue and abortifacient, the essential oil should not be used internally during pregnancy (*50–52*).

Warnings

Essential oils should be used with caution in children. Keep out of the reach of children.

Precautions

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to a lack of safety data, the essential oil should be administered internally only under the supervision of a health-care provider.

Paediatric use

Owing to a lack of safety data, the essential oil should be administered internally only under the supervision of a health-care provider.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; or teratogenic effects during pregnancy.

Dosage forms

Essential oil (*15*). Store in a well-closed container, in a cool, dry place, protected from light (*4*).

Posology

(Unless otherwise indicated)

Essential oil by inhalation, 0.06–0.2 ml three times per day (*7*); internally, 1–4 drops (approximately 20–80.0 mg) on a sugar cube per day (*24*).

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Flos Lavandulae

Definition

Flos Lavandulae consists of the dried flowers of *Lavandula angustifolia* Mill. (Lamiaceae) (*1–3*).

Synonyms

Lavandula officinalis Chaix, *L. spica* Loisel., *L. vera* DC, *L. vulgaris* Lam. (*1, 4, 5*). Lamiaceae are also known as Labiatae. In most formularies and older reference books, *Lavandula officinalis* Chaix is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Lavandula angustifolia* Mill. is the legitimate name for the species (*5, 6*).

Selected vernacular names

Al birri, alhucema, arva neh, aspic, broad-leaved lavenda, common lavender, Echter Lavendel, English lavender, espi, espic, espliego común, firigla, frigous, garden lavendar, grando, hanan, hanene, hzama, khazama, khirii, khouzamaa, khouzami, khuzama, khuzama fassiya, khuzama zerqua, Kleiner Speik, Lavanda, lavande, lavande femelle, lavande véritable, lavando, lavandula vraie, Lavendel, lavender, lawanda, lófinda, ostoghodous, postokhodous, spigandos, true lavender (*1, 2, 5–9*).

Geographical distribution

Indigenous to the northern Mediterranean region. Cultivated in southern Europe and in Bulgaria, Russian Federation, United States of America and the former Yugoslavia (*5, 10*).

Description

An aromatic shrub, 1–2 m high. Branches grey-brown to dark brown with long flowering and short leafy shoots, bark longitudinally peeling. Leaves clustered on leafy shoots, widely spaced on flowering shoots; petiole very short; blade linear-lanceolate to linear, 17 mm long, 2 mm wide on leafy shoots, 2–6 cm long, 3–6 mm wide on flowering shoots; grey

stellate tomentose, base attenuate, margin entire, revolute, apex obtuse. Inflorescence a crowded, interrupted or nearly continuous spike, 2–8 cm long; verticillasters numerous, with 6–10 flowers, upper ones densely crowded; peduncle about three times longer than the spike; bracts papery, rhombic-ovate, 3–8 mm long, rust coloured when dry; bracteoles absent or up to 2.5 mm long, pedicel 1.0–1.5 mm long; calyx 4–7 mm long, densely grey stellate tomentose outside, with 13 longitudinal ribs, upper lip entire, appendage obcordate, lower lip four-toothed; corolla 10–12 mm long, blue, base subglabrous, throat and limb glandular hairy, upper lips straight, lower lips spreading. Nutlets narrowly cylindrical (*5*).

Plant material of interest: dried flowers

General appearance

Consists mainly of tubular-ovoid, ribbed, bluish-grey calices with five teeth, four of which are short, while the fifth forms an oval or cordate projecting lip. Petals, much crumpled, are fused into a tube with a lower lip consisting of three small lobes and an upper lip comprising two larger erect lobes; the colour varies from deep bluish grey to a discoloured brown. Corolla contains four stamens and a superior ovary (*10*).

Organoleptic properties

Odour: fragrant, aromatic; taste: aromatic, bitter, somewhat camphoraceous (*1, 2*).

Microscopic characteristics

Calyx and corolla bear glandular hairs with a very short unicellular stalk and a head of four to eight cells, of a labiaceous type, and characteristic branching unicellular and multicellular non-glandular hairs with pointed ends and a somewhat streaked or warty cuticle. Corolla bears also, on the inner surface at the throat, characteristic glandular hairs with a unicellular, glandular head and a bicellular stalk, its basal cell being long and knotted and the other cell short and cylindrical. Anthers covered with whip-shaped, unicellular, non-glandular trichomes; pollen grains, almost rounded, with six germ pores (*1*).

Powdered plant material

Grey-blue with fragments of calyx, elongated epidermal cells with wavy anticlinal walls, and multicellular non-glandular covering trichomes. Encapsulated labiate oil glands. Corolla fragments, almost oval and slightly wavy-walled epidermal cells, labiate oil glands and branched covering hairs; unicellular glandular hairs. Pollen grains spherical to ellipsoidal, 24–30 µm in diameter, with six furrows, six germ pores and lines of pits

radiating from the poles. Leaf fragments, almost straight-walled epidermal cells, covering branched trichomes and labiate oil glands, glandular hairs with a unicellular stalk and a bicellular head (*11*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), microchemical tests (*2*), and thin-layer chromatography for the presence of linalyl acetate and linalool (*3*, *12*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2.0% (*3*).

Total ash

Not more than 9.0% (*3*).

Acid-insoluble ash

Not more than 1.0% (*2*).

Water-soluble extractive

Not less than 18.0% (*2*).

Alcohol-soluble extractive

Not less than 12.0% (*2*).

Moisture

Not more than 10.0% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

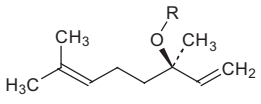
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*13*).

Other purity tests
Chemical tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 1.3% (v/w) essential oil determined by steam distillation (*3*).

Major chemical constituents
Contains 1.0–3.0% essential oil, of which the major constituents are linalyl acetate (30–55%) and linalool (20–50%). Other constituents include β-ocimene, 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol), camphor and caryophyllene oxide (*6, 9, 10*). The structures of linalyl acetate and linalool are presented below.



and enantiomer

linalool R = H

linalyl acetate R = CO-CH3

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Symptomatic treatment of restlessness, insomnia, and as a carminative and antispasmodic for gastrointestinal disorders of nervous origin (*10, 16*). Externally in balneotherapy for the treatment of cardiovascular disorders (*10, 16*).

Uses described in traditional medicine
As a diuretic and an emmenagogue, and for the treatment of burns, diarrhoea, headaches, sore throats and wounds (*10*).

Pharmacology
Experimental pharmacology
Antimicrobial activity
Aqueous, chloroform, hexane and methanol extracts of Flos Lavandulae, 60.0 µg/ml, inhibited the growth of *Streptococcus pneumoniae* in vitro

(*17*). A methanol extract of the flowers inhibited the growth of *Helicobacter pylori* (the bacterium associated with peptic ulcer disease) in vitro, minimum inhibitory concentration 100.0 µg/ml (*18*).

Antioxidant activity
A 50% ethanol extract of the flowers had antioxidant activity in vitro, median effective dose 45.0 mg/ml (*19*).

Antiulcer activity
Intragastric administration of 400.0 mg/kg body weight (bw) of an 80% ethanol extract of the flowers to mice significantly ($P < 0.05$) reduced ethanol-induced gastric ulcerations by 62.9% (*20*).

Uterine stimulating activity
A hot aqueous extract of the flowers (dose not specified) stimulated uterine contractions in isolated pregnant guinea-pig uterus (*21*).

Anticonvulsant and sedative activities
Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents protected against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*22, 23*). In mice, intraperitoneal administration of 2.5 g/kg bw of linalool interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*24*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes, suggesting interference of glutamatergic transmission. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool reduced potassium-stimulated glutamate release (*25*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission.

Adverse reactions
No information available.

Contraindications
Flos Lavandulae is contraindicated in cases of known allergy to the plant material. Owing to their traditional use as an emmenagogue and abortifacient, the flowers should not be used during pregnancy (*21, 26*).

Warnings
No information available.

Precautions

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic effects during pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried flowers, tablets, capsules, fluidextract, syrup, tincture and tonics (*10*). Store in a well closed container, in a cool, dry place, protected from light (*1*).

Posology

(Unless otherwise indicated)

Internally as a tea, dried flowers, 1–2 teaspoonfuls per cup, three times per day; tincture (1:5) in 60% ethanol, 2–4 ml three times per day (*11*). Externally as bath therapy, dried flowers, 20–100 g per 20 l of water (*16*).

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Strobilus Lupuli

Definition

Strobilus Lupuli consists of the dried strobiles or inflorescences of the female plants of *Humulus lupulus* L. (Cannabaceae) (*1, 2*).

Synonyms

Humulus lupulus L. var. *cordifolius* (Miq.) Maxim. in Franch. et Sav. = *H. cordifolius* Miq., *H. lupulus* L. var. *lupuloides* E. Small = *H. americanus* Nutt., *H. lupulus* L. var. *lupuloides* = *Cannabis lupulus* (L.) Scop., *H. lupulus* L. var. *brachystachyus* Zapalowicz, *H. lupulus* L. var. *neomexicanus* Nelson et Cockerell = *H. neomexicanus* (Nelson et Cockerell) Rydberg, *H. volubilis* Salisb., *H. vulgaris* Gilib., *Lupulus communis* Gaertn., *L. humulus* Mill., *L. scandens* Lam. (*3*).

Selected vernacular names

Betiguera, bine, common hops, Echter Hopfen, European hops, hachichet addinar, hoblon, hombrecillo, hop, hop vine, Hopfen, hops, houblon, houblon grimpant, houblon vulgaire, humulus, lupio, luppulo, lupol, lupulin, lupulo, pijiuha, razak, vidarria, vigne du nord, xianshema (*3–6*).

Geographical distribution

Distributed in Europe, Asia and North America. Cultivated widely in the temperate zones of the world (*5, 7*).

Description

A perennial, dioecious, twining herb, up to 6 m high. Aerial parts consist of several long, angular, rough-hairy, entwining stems bearing cordate, palmate, three-lobed, occasionally five- to seven-lobed, scabrous, dark green, stipulate leaves. Staminate flowers, with five bracts and five stamens, borne in axillary panicles. Pistillate flowers pale green, each consisting of an entire cup-like perianth and a unilocular ovary with a single ovule, and two long stigmas, borne on a leafy conical catkin. Fruits are ovate to ovate-cylindrical strobiles consisting of a flexuous rachis bearing

yellowish-green to pale brown, ovate, membranous, scaly bracts, each enclosing a brown glandular achene (*7*).

Plant material of interest: dried strobiles

General appearance

Strobiles ovoid-cylindrical or cone-like, leafy, 3–4 cm long and up to 3 cm wide, consisting of a narrow, hairy, flexuous rachis and numerous imbricated, yellowish-green to dusky yellow, obliquely ovate, membranous bracts, the base of each with numerous orange to yellowish-orange, glandular trichomes, and frequently infolded on one side, enclosing a light brown subglobular glandular achene (*7*).

Organoleptic properties

Odour: strong, characteristically aromatic, becoming valerian-like on ageing; taste: aromatic, bitter (*7*).

Microscopic characteristics

Epidermal cells of stipules and bracteoles irregularly polygonal with sinuous anticlinal walls, usually thin, occasionally slightly beaded and thickened; rare anomocytic stomata and cicatrices. Mesophyll seen in section shows small cluster crystals of calcium oxalate; glandular trichomes with a two-celled stalk and a spherical glandular head of eight cells; numerous large yellow glands, 100–250 µm in diameter, each consisting of thin-walled cells with a dome-shaped cuticle, circular in surface view and cup-shaped in side view, attached to the stipule or bracteole by a short two-celled stalk. Epicarp of fruit consists of sclerenchymatous cells, irregularly elongated, pale brown with thick walls showing numerous small pits and striations (*1*).

Powdered plant material

Greenish-yellow; fragments of bracts and bracteoles covered by polygonal, irregular epidermal cells with wavy walls; unicellular, conical, straight or curved covering trichomes with thin, smooth walls; rare anomocytic stomata; fragments of mesophyll containing small calcium oxalate cluster crystals; many characteristic orange-yellow glandular trichomes with short, bicellular, biseriate stalks, bearing a partial widening into a cup, 150–250 µm in diameter, made up of a hemispherical layer of secretory cells with a cuticle that has been detached and distended by the accumulation of oleoresinous secretions; fragments of elongated sclerenchymatous cells of the testa with thick walls showing striations and numerous pits (*2*).

General identity tests

Macroscopic and microscopic examinations (*1*, *7*), and thin-layer chromatography (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*8*).

Foreign organic matter

Not more than 2% (*1*, *2*).

Total ash

Not more than 12% (*2*).

Acid-insoluble ash

Not more than 5% (*1*).

Water-soluble extractive

Not less than 10% (*2*).

Alcohol-soluble extractive

Not less than 25% in 70% (v/v) ethanol (*2*).

Loss on drying

Not more than 10% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

Other purity tests

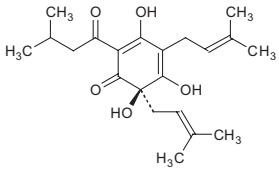
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

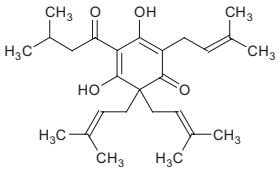
High-performance liquid chromatography for bitter substances and xanthohumol (*3*).

Major chemical constituents

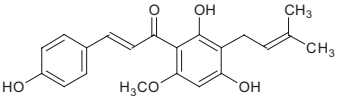
The major constituents are bitter substances (15–25%) in the resins. The resins are differentiated into hard (petroleum-ether insoluble) and soft resins. The lipophilic soft resins contain mainly α-acids (e.g. α-humulene (2,6,9-humulatriene) and related humulones) and β-acids (lupulones). The major chemical constituents of the soft resins are humulone and lupulone and their related derivatives, 2–10% and 2–6%, respectively. The hard resin contains a hydrophilic fraction, δ-resin, and a lipophilic fraction, γ-resin. The essential oil (0.3–1.0%) contains mainly monoterpenes and sesquiterpenes such as β-caryophyllene, farnesene, humulene and β-myrcene (*3, 5, 6, 11, 12*). The essential oil also contains traces of 2-methylbut-3-ene-2-ol, which increases in amount to a maximum of 0.15% after storage of the strobiles for 2 years, owing to degradation of the humulones and lupulones. Other constituents include the chalcone xanthohumol, prenylflavonoids and other flavonoids (e.g. kaempferol, rutin) and tannins (*3, 6, 13, 14*). Representative structures are presented below.



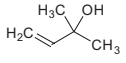
humulone



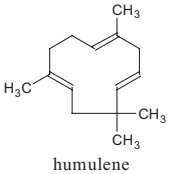
lupulone



xanthohumol



2-methylbut-3-en-2-ol



humulene

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As a sedative for the treatment of nervous tension and insomnia. Treatment of dyspepsia and lack of appetite (*5, 15–17*).

Uses described in traditional medicine

Treatment of abdominal cramps, anaemia, bacterial infections, dermatitis, diarrhoea, dysmenorrhoea, leukorrhoea, migraine and oedema (*6*). As an analgesic, anthelminthic, antipyretic, aphrodisiac, carminative, depurative, digestant, diuretic, diaphoretic and tonic (*6*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

The essential oil of the strobiles, 2.5 µl/disc, inhibited the growth of *Staphylococcus aureus*, *Bacillus subtilis, Trichophyton interdigitale, Candida albicans* and *Escherichia coli* (*18*). Other researchers reported antimicrobial effects against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and the fungus *Trichophyton mentagrophytes* var. *interdigitale* at a concentration of 20 mg/ml, but no activity against a Gram-negative bacterium (*Escherichia coli*) or the yeast *Candida albicans* (*19*). A methanol extract of the strobiles inhibited the growth of *Helicobacter pylori*, minimum inhibitory concentration (MIC) range 63.0–130.0 µg/ml (*20*). Lupulone and humulone were isolated from the methanol extract as the active constituents. The MIC range for lupulone was estimated at 0.63–13.0 µg/ml (*20*). A decoction of the strobiles and lupulone inhibited the growth of *Mycobacterium tuberculosis*, MIC 1.0–10 µg/ml for lupulone and 7.5 µg/ml for the decoction (*17*).

The antibacterial activity of the weak acids derived from Strobilus Lupuli increases with decreasing pH of the medium. The MICs of these compounds against *Lactobacillus brevis* IFO 3960 at a pH range of 4–7 suggest that undissociated molecules are mainly responsible for the inhibition of bacterial growth (*21*).

Anti-oedema activity

External application of a methanol extract of Strobilus Lupuli to mouse ears, 2.0 mg/ear, inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced inflammation by 90% (*22*). Humulone, 1 mg/animal, inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate and ear oedema induced by arachidonic acid in mice (*23*).

Antioxidant activity

A methanol extract of the strobiles had antioxidant and radical scavenging activities in vitro (*24, 25*).

Central nervous system depressant activity

Intraperitoneal administration of 100.0 mg/kg body weight (bw) of a methanol extract of the strobiles had analgesic effects, as shown by the increased latency of licking the forepaws in the hot-plate test in mice (*26, 27*). Intraperitoneal administration of the extract also reduced spontaneous motor activity and decreased performance on an animal coordination meter (Rota-Rod) by 59% at doses above 250.0 mg/kg bw. At a dose of 250.0 mg/kg bw the extract also produced a dose-dependent increase in pentobarbital-induced sleeping time in mice (*26, 27*). However, oral doses of up to 500.0 mg/kg of an ethanol extract of the strobiles did not have any sedative effects in mice (*28*). Oral administration of a methanol extract of the strobiles, 500.0 mg/kg bw, inhibited pentylenetetrazole-induced convulsions and reduced body temperature in mice (*26, 27*). Intraperitoneal administration of 0.8 g/kg bw of the 2-methylbut-3-ene-2-ol, extracted from the essential oil of the strobiles to mice induced narcosis lasting 8 hours (*29*). Intraperitoneal administration of 206.5 mg/kg bw of 2-methylbut-3-ene-2-ol to rats caused a 50% decrease in motility (*30*).

Administration of an essential oil of the strobiles via nasogastric tube (dose not specified) induced central nervous system depression in pigeons (*31*). Intramuscular administration of an essential oil (dose not specified) to mice had unspecified sedative activity (*29*). A commercial extract (no further information available) of the strobiles, ≤2 µg/ml, bound to the γ-aminobutyric acid, the glutamate and the *N*-methyl-D-asparate receptors, as well as the chloride ion channel and glycine receptors in vitro (*32*).

Estrogenic activity

Subcutaneous administration of an aqueous or a 95% ethanol extract of the strobiles at various concentrations had estrogenic effects in mice and rats as assessed by the Allen-Doisy assay (which measures vaginal cornification in ovariectomized animals) (*33–37*). The activity was reported to be equivalent to that of 20–300 µmol/g bw of 17-β-estradiol (*33*). Using the Allen-Doisy assay, the estrogenic hormonal activity of a lipophilic extract of the strobiles was greater than that of an aqueous extract of 17-β-estradiol equivalents (1250 µg/g bw compared with 30–300 µg/g bw) (*35*). However, other investigators reported no estrogenic effects in mice following subcutaneous administration of doses of up to 51.0 mg/kg bw (*38, 39*).

Subcutaneous administration of 5.0 mg of an alcohol extract of the strobiles to rats had a luteal suppressant effect (*40*). An extract of the

strobiles (unspecified) administered to ovariectomized rats in the diet (dose not specified) bound to estrogen receptors in vitro, and increased the concentration of hepatic ceruloplasmin messenger RNA, indicating an hepatic estrogenic response (*41*).

A polyphenolic fraction isolated from an alcohol extract of the strobiles stimulated the activity of alkaline phosphatase in human endometrial cells, Ishikawa variety I in vitro (*42*). A phytoestrogen, 8-prenylnaringenin, isolated from the polyphenolic fraction, 1 nmol/l, bound to estrogen receptors isolated from rat uteri (*42*). Methanol extracts of the strobiles competitively bound to estrogen receptors-alpha and -beta from rat uteri (*43*). The extracts also induced the expression of alkaline phosphatase activity and upregulated progesterone receptor messenger RNA (*43*).

Miscellaneous activity

Intragastric administration of three doses of an essential oil of the strobiles, 30 mg/animal, given over 2 days, stimulated the activity of glutathione-*S*-transferase in the liver and intestine of mice (*44*). Six flavonoid compounds isolated from the strobiles, 0.1–100.0 µmol/l, inhibited the growth of human breast cancer (MCF-7), colon cancer (HT-29) and ovarian cancer (A-2780) cells in vitro (*45*). Flavonoid compounds isolated from the strobiles, namely xanthohumol, isoxanthohumol and 8-prenylnaringenin, 10.0 µmol/l, inhibited the 7-ethoxyresorufin-*O*-deethylase activity of the CYP1A1 and CYP1A2 isozymes of cytochrome P450 (*46*).

Toxicology

The median lethal dose (LD_{50}) of orally administered ethanol extracts of the strobiles or lupulones in mice was found to be 500.0–3500.0 mg/kg bw (*29*). The oral LD_{50} in rats was 2700.0 mg/kg bw (*29*). The oral LD_{50} for lupulone was 525.0 mg/kg bw in mice and 1800.0 mg/kg bw in rats (*3*). The intraperitoneal LD_{50} of an ethanol extract of the strobiles in mice was 175.0 mg/kg bw (*17*).

Clinical pharmacology

In a small study without controls, oral administration of 250.0 mg of a lipophilic concentrate of the strobiles daily for 5 days to 15 healthy volunteers had no sleep-inducing effects (*47*).

Adverse reactions

Strobilus Lupuli may cause drowsiness (*31*).

Contraindications

Strobilus Lupuli is contraindicated in cases of known allergy to the plant material.

Warnings

No information available.

Precautions

Drug interactions

While no drug interactions have been reported, flavonoid constituents of Strobilus Lupuli have been shown to inhibit the activity of cytochrome P450, and concurrent administration of the strobiles with prescription drugs metabolized by these enzymes may adversely influence the pharmacokinetics of these drugs.

Carcinogenesis, mutagenesis, impairment of fertility

Subcutaneous administration of 20.0–50.0 mg/kg bw of purified fractions of the strobiles twice daily for 3 days to female rats pretreated by subcutaneous injection with 25 IU of pregnant mare's serum gonadotrophin did not induce any changes in uterine weight, but ovarian weight decreased significantly ($P < 0.05$) (*48*).

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried strobiles and dried extracts for infusions and decoctions, dry extracts, fluidextracts, and tinctures (*7, 16*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Cut or powdered strobiles or dry powder for infusion, decoctions and other preparations, single dose of 0.5 g; liquid and solid preparations for internal use, infusion or decoction, 0.5 g in 150 ml of water; fluidextract 1:1 (g/ml) 0.5 ml; tincture 1:5 (g/ml) 2.5 ml; native dry extract 6–8:1 (w/w) 0.06–0.08 g (*16*).

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Gummi Myrrha

Definition

Gummi Myrrha consists of the air-dried oleo-gum resin exudates from the stems and branches of *Commiphora molmol* Engler (Burseraceae) and other related *Commiphora* species (*1–4*), including *C. abyssinica* Engl., *C. erythraea* and *C. schimperi* Engl. (*5*), but excluding *C. mukul*.

Synonyms

For *Commiphora molmol* Engl.: *Balsamodendron myrrha* Nees, *Commiphora myrrha* Holm, *C. myrrha* (Nees) Engl. var. *molmol* Engl. (*2, 6*).

Selected vernacular names

Abyssinian myrrh, arbre à myrrhe, bal, barakande, bisabol myrrh, bol, bola, dashi 'biskiti, gandharsh, guban myrrh, habaq-hagar-ad, heerbol, heerabol myrrh, hirabol myrrh, Männliche myrrhe, mbebe, mbele, mo yao, morr, morrh, mur, murr, myrr, myrrh, Myrrhenbaum, myrrha, molmol, myrrhe des somalis, ogo myrrh, turari, Somali myrrh (*1, 2, 6–11*).

Geographical distribution

Various *Commiphora* species are indigenous to arid and tropical regions of Africa. *Commiphora molmol* is indigenous to Somalia and is cultivated in the Arabian Peninsula and North Africa and in Ethiopia, India, Kenya and United Republic of Tanzania (*1, 2, 9*).

Description

Commiphora species are shrubs or small trees, about 3 m high, with rounded tops, thick trunks, dark brown bark and large, sharply pointed thorns on the stem. Branches numerous, irregular or rough, stunted and spiny. Leaves unequal, ternate, alternate. Flowers small, dioecious, yellow-red fascicled, polygamous, arranged in terminal panicles. Calyx tubular, teeth usually four, valvate petals usually found inserted on the edge of the disk; stamens 8–10 on disk alternately long and short filaments, dialated below. Fruits are oval-lanceolate drupes, about 0.3 cm

long. When stems are damaged or incised, oleo-gum resins exude from the schizogenous resin ducts (*1, 2, 7, 10*).

Plant material of interest: dried oleo-gum resin

General appearance

Rounded or irregular tears or lumps of agglutinated tears of variable sizes; brownish-yellow to reddish-brown or almost black. The surface is mostly covered with a greyish or yellowish powder; the internal surface is yellowish or reddish-brown, sometimes marked with white spots or lines; brittle; fracture, waxy, granular, conchoidal and yields thin translucent fragments (*1, 3, 7, 10*).

Organoleptic properties

Odour: characteristic, aromatic, balsamic; taste: aromatic, bitter, acrid (*1–3, 7, 10*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Macroscopic (*1, 7, 10*) and microscopic (*10*) examinations; microchemical and spectroscopic tests (*1, 3, 7, 12*), and thin-layer chromatography (*2–4, 13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Total ash

Not more than 10.0% (*1*). Not more than 7.0 % (*4*).

Acid-insoluble ash

Not more than 5.0% (*1*).

Water-soluble extractive

Not less than 48% (*2*).

Alcohol-insoluble residue

Not more than 70.0% (*1, 4*).

Moisture
Not more than 15.0% (*4*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*14*).

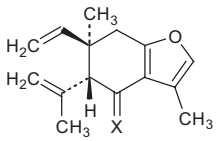
Other purity tests
Chemical and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays
Not less than 6% essential oil (*3*). Qualitative and quantitative high-performance liquid chromatography for furanosesquiterpenes (*17*).

Major chemical constituents
The oleo-gum resin obtained from *C. molmol* contains: resins (25–40%), essential oil (3–8%) and a water-soluble gum (30–60%) (*1, 18*). The gum is composed of 20% proteins and 65% carbohydrates made up of galactose, 4-*O*-methylglucuronic acid and arabinose. The major constituents of the essential oil are furanosesquiterpenes (*10*), and the monoterpenes α-, β- and γ–bisabolene. Representative structures are presented below.

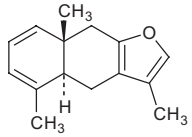
Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Topical treatment of mild inflammations of the oral and pharyngeal mucosa (*3, 19, 20*). As a gargle or mouth rinse for the treatment of aphthous ulcers, pharyngitis, tonsillitis, common cold and gingivitis (*3, 21*).

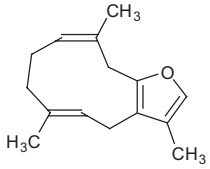


curzerene X = H_2
curzerenone X = O

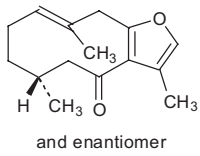
and enantiomer



furanoeudesma-1,3-diene

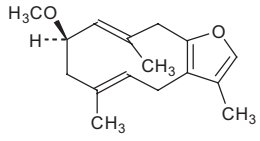


furanodiene



and enantiomer

4,5-dihydrofuranodien-6-one



2-methoxyfuranodiene

Uses described in traditional medicine

As an emmenagogue, expectorant and antidote for poisons, and to inhibit blood coagulation. Treatment of menopausal symptoms, arthritic pain, diarrhoea, fatigue, headache, jaundice and indigestion, and applied topically for treatment of burns and haemorrhoids (*9, 11, 22, 23*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of an aqueous suspension of Gummi Myrrha, 10% in saline solution, 10.0 ml/kg body weight (bw) had analgesic effects in mice, as assessed by the hot-plate test (*24*). Intragastric administration of 50.0 mg/kg bw of a sesquiterpene, furanoeudesma-1,3-diene, isolated from the resin also had analgesic effects in mice as measured by the acetic acid writhing test (*24*). Intragastric administration of 400.0 mg/kg bw of a 100% ethanol extract of the resin reduced writhing induced by acetic acid in mice by 25% (*25*). Intragastric administration of 500.0 mg/kg bw of a petroleum ether extract or a 95% ethanol extract of the resin significantly ($P < 0.05$) suppressed yeast-induced pyrexia in mice (*26, 27*).

Anticoagulant activity

Intraperitoneal administration of 100.0 mg/kg bw of an ethyl acetate extract of the resin inhibited platelet aggregation in mice. However, an aqueous extract of the resin given by the same route was not active (*28*). Intraperitoneal administration of 100.0 mg/kg bw of an ethyl acetate extract of the resin, had antithrombotic activity in mice (*29*).

Antihyperglycaemic activity
Intragastric administration of 10.0 ml/kg bw of a hot aqueous extract of the resin per day for 7 days, reduced blood glucose levels in diabetic rats (*30*). Intragastric administration of 150–175.0 mg/kg bw of two furanosesquiterpenes isolated from the resin significantly ($P < 0.0036$–0.0009) reduced blood glucose levels in genetically altered obese diabetic mice, measured 27 hours after administration (*31*).

Anti-inflammatory activity
Intragastric administration of 400.0 mg/kg bw of an aqueous extract of the resin to rats significantly ($P < 0.05$) reduced carrageenan-induced footpad oedema by up to 59% (*32*). Intragastric administration of 400.0 mg/kg bw of a petroleum ether extract of the resin per day for 18 days to rats with Freund's adjuvant-induced arthritis significantly ($P < 0.05$) reduced the development of inflammation (*32*). Intragastric administration of 80.0 mg/kg bw of a petroleum ether extract of the resin inhibited carrageenan-induced footpad oedema in rats (*33*). Intraperitoneal administration of 200–400.0 mg/kg bw of a 100% ethanol extract of the resin reduced xylene-induced ear inflammation in mice by 50% (*25*). Intragastric administration of 500.0 mg/kg bw of a petroleum ether extract of the resin reduced carrageenan-induced footpad oedema and cotton pellet-induced granuloma in rats (*26*).

Cytoprotectant activity
Intragastric administration of 250.0 mg/kg bw of an aqueous suspension of the resin reduced the formation of ulcers induced by ethanol, sodium chloride and indometacin in rats by increasing the production of gastric mucus (*34*).

Toxicology
An ethanol extract of the resin was administered to rats by gastric lavage (1000.0 mg/kg bw), intramuscular injection (500.0 mg/kg bw) or intraperitoneal injection (250.0 mg/kg bw) daily for 2 weeks. Depression, huddling, jaundice, ruffled hair, hepatonephropathy, haemorrhagic myositis and patchy peritonitis at the injection site, and death were observed. Increases in serum alanine phosphatase, alanine transferase activities, bilirubin, cholesterol and creatinine concentrations, and decreases in total protein and albumin levels, macrocytic anaemia and leukopenia were also seen. When the doses were halved, the adverse effects were reduced (*35*).

The oral lethal dose of the essential oil is 1.65 g/kg bw in rats (*36*). However, no deaths were reported in mice after intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the resin (*27*).

Intragastric administration of 1.0–5.0 g/kg bw of the resin per day to Nubian goat kids caused grinding of teeth, salivation, soft faeces, inappetence, jaundice, dyspnoea, ataxia and recumbency. Death occurred between days 5 and 16. Enterohepatonephrotoxicity was accompanied by anaemia, leukopenia, increases in serum alanine phosphatase activity and concentrations of bilirubin, cholesterol, triglycerides and creatinine, and decreases in total protein and albumin. An oral dose of 0.25 g/kg bw per day was not toxic (*37*).

In acute (24-h) and chronic (90-day) oral toxicity studies in mice, the resin was administered at doses of 0.5 g/kg bw, 1.0 g/kg bw or 3.0 g/kg bw, and 100.0 mg/kg bw per day, respectively. No significant increase in mortality was observed in either study. In the chronic study, however, there was an increase in body weight and increases in the weight of the testes, caudae epididymides and seminal vesicles in treated animals as compared with untreated controls. Treated animals also showed an increase in red blood cells and haemoglobin levels. No spermatotoxic effects were observed in treated animals (*38*).

Clinical pharmacology

No information available.

Adverse reactions

Topical application of a diluted (8%) solution of an essential oil obtained from the resin was non-irritating, non-sensitizing and non-phototoxic when applied to human skin (*36*). Application of an unspecified extract of the resin to human skin caused contact dermatitis (*39–41*).

Contraindications

Gummi Myrrha is used in traditional systems of medicine as an emmenagogue, and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, Gummi Myrrha should not be used during pregnancy (*42, 43*).

Warnings

Use of the undiluted tincture may give rise to a transient burning sensation and irritation of the palate (*3*).

Precautions

Drug interactions

Although no drug interactions have been reported, internal ingestion of Gummi Myrrha may interfere with existing antidiabetic therapy owing to

the ability of the resin to reduce blood glucose levels. Patients taking anticoagulant drugs or with a history of bleeding disorders should consult their health-care provider prior to using the resin.

Carcinogenesis, mutagenesis, impairment of fertility
An aqueous extract of the resin, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98 and TA100 (*44*). Intraperitoneal administration of an aqueous extract of the resin at doses 10–40 times the normal therapeutic dose did not have mutagenic effects (*44*). A hot aqueous extract of the resin, 40.0 mg/plate, inhibited aflatoxin B1-induced mutagenesis in *S. typhimurium* strains TA98 and TA100 (*45*). The genotoxic, cytotoxic and antitumour properties of the resin were investigated in normal mice and mice bearing Ehrlich ascites carcinoma cells. The genotoxic and cytotoxic activity was evaluated on the basis of the frequency of micronuclei and the ratio of polychromatic to normochromatic cells in the bone marrow of normal mice. Intragastric administration of 125.0–500.0 mg/kg bw of the resin did not have clastogenic effects, but was cytotoxic in normal mice. In the mice bearing tumours, the resin had antitumour activity, and was reported to be as effective as the antitumour agent cyclophosphamide (*46*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
Owing to the lack of data concerning the safety and efficacy of Gummi Myrrha, it should not be used by nursing mothers without consulting a health-care practitioner.

Paediatric use
Owing to the lack of data concerning the safety and efficacy of Gummi Myrrha, it should not be administered to children without consulting a health-care practitioner.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms
Powdered resin, capsules, myrrh tincture, and other galenical preparations for topical use (*20*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Myrrh tincture (1:5 g/ml, 90% ethanol), undiluted tincture applied to the affected area two or three times per day; mouth rinse or gargle, 5–10 drops of the tincture in a glass of water (*20*); mouthwash or gargle solution, 30–60 drops of the tincture in a glass of warm water (*19*); paint, undiluted tincture applied to the affected areas on the gums or the mucous membranes of the mouth with a brush or cotton swab, two or three times per day (*19*); dental powder, 10% powdered oleo-gum resin (*20*).

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Herba Passiflorae

Definition
Herba Passiflorae consists of the dried aerial parts of *Passiflora incarnata* L. (Passifloraceae) (*1–3*).

Synonyms
Granadilla incarnata Medik., *Passiflora kerii* Spreng. (*4*).

Selected vernacular names
Apricot vine, flor de la pasión, Fleischfarbene Passionsblume, fiore della passione, fleur de la passion, grenadille, maracujá, may apple, may flower, may-pop, pasionaria, passiflora, passiflora roja, passiflore, passion vine, rose-coloured passion flower, water lemon, white passion flower, wild passion flower (*2, 4–6*).

Geographical distribution
Indigenous to North America (*5, 7, 8*).

Description
A perennial, creeping herb, climbing by means of axillary tendrils. Leaves alternate, palmately three to five serrate lobes. Flowers large, solitary, with long peduncles, whitish, with a triple purple and pink crown. Fruits are ovate berries containing numerous ovoid, flattened seeds covered with a yellowish or brownish aril (*7*).

Plant material of interest: dried aerial parts
General appearance
Stems lignified, green, greyish-green or brownish, usually less than 5 mm in diameter; rounded, longitudinally striated and often hollow. Leaves alternate with furrowed, often twisted petioles, possessing two extra-floral nectaries at the apex; lamina 6–15 cm long, broad, green to brownish green, palmate with three to five lanceolate lobes covered with fine hairs

on the lower surface; margin serrate. Tendrils borne in leaf axils, smooth, round and terminating in cylindrical spirals. Flowers 5–9 cm in diameter with peduncles up to 8 cm long, arising in leaf axils; five, white, elongated petals; calyx of five thick sepals, upper surface green and with a horn-like extension; involucre of three pointed bracts with papillose margins; five large stamens, joined at the base and fused to the androgynophor; ovary greyish-green, superior; style hairy with three elongated stigmatic branches. Fruits 4–5 cm long, oval, flattened and greenish-brown containing numerous seeds 4–6 mm long, 3–4 mm wide and 2 mm thick, with a brownish-yellow, pitted surface (*2*).

Organoleptic properties

No distinctive odour; taste: bitter (*2*).

Microscopic characteristics

Transverse section of older stem shows epidermis of isodiametric cells with strongly thickened, convex external walls; some cells containing crystals of calcium oxalate, others developing uniseriate trichomes two to four cells long, terminating in a rounded point and frequently hooked; hypodermis consisting of a layer of tangentially elongated cells, outer cortex with groups of collenchyma, containing cells with brown, tanniferous contents; pericycle with isolated yellow fibres and partially lignified walls; inner cortex of parenchymatous cells containing cluster crystals of calcium oxalate; xylem consisting of groups of vessels up to 300 µm in diameter with pitted, lignified tracheids; pith of lignified parenchyma containing numerous starch grains 3–8 µm in diameter, simple or as aggregates. Leaf upper and lower epidermis shows sinuous anticlinal cell walls; numerous anomocytic stomata in the lower epidermis, which also has numerous uniseriate covering trichomes of one to three cells, terminal cells comparatively long, pointed and curved; groups of brown tannin cells occur in the marginal teeth and in the mesophyll; cluster crystals of calcium oxalate 10–20 µm in diameter isolated in the mesophyll or arranged in files associated with the veins. Sepal upper epidermis has large, irregular, polygonal cells with some thickened walls, striated cuticle, rare stomata and numerous small crystals of calcium oxalate; lower epidermis comprises two layers, the outer layer consisting of polygonal cells with numerous stomata and small crystals of calcium oxalate, the inner layer of smaller polygonal cells. Epidermal cells of the petals papillose, especially in the filiform appendices. Pollen grains 65–75 µm in diameter, with a cross-ridged surface and three acuminate germinal pores. Pericarp composed of large cells with few stomata and groups of calcium oxalate crystals; endocarp of thickened, sclerous cells (*2*).

Powdered plant material

Light green and characterized by fragments of leaf epidermis with sinuous cell walls and anomocytic stomata; numerous cluster crystals of calcium oxalate isolated or aligned along the veins; many isolated or grouped fibres from the stems associated with pitted vessels and tracheids; uniseriate trichomes with one to three thin-walled cells, straight or slightly curved, ending in a point or sometimes a hook. If flowers are present, papillose epidermis of the petals and appendages and pollen grains with a reticulate exine. If mature fruits are present, scattered brown tannin cells and brownish-yellow, pitted fragments of the testa (*3*).

General identity tests

Macroscopic and microscopic examinations (*2, 3*), and thin-layer chromatography for the presence of flavonoids (*2, 3, 9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Chemical

Contains not more than 0.01% harman alkaloids (*11*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 13% (*3*).

Acid-insoluble ash

Not more than 3.0% (*2*).

Water-soluble extractive

Not less than 15% (*2*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia*

(*12*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 1.5% of total flavonoids, expressed as vitexin, determined by spectrophotometry (*3*). A high-performance liquid chromatography method for flavonoids is also available (*14*).

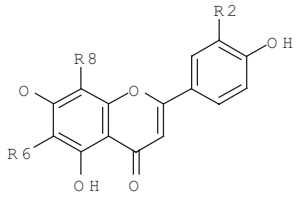
Major chemical constituents

The major constituents are flavonoids (up to 2.5%) with the principal compounds being the *C*-glycosyl of apigenin (R2 = H) and luteolin (R2 = OH), including mono-*C*-glucosyl derivatives isovitexin (up to 0.32%), iso-orientin and their 2''-β-D-glycosides, and di-*C*-glycosyl derivatives schaftoside (up to 0.25%), isoschaftoside (up to 0.15%) and swertisin (*1, 15, 16*). Also found are di-*C*-glucosyl derivatives vicenin-2 and lucenin-2 and small amounts of mono-*C*-glucosyl derivatives orientin and vitexin (*1*). Other chemical constituents include maltol (3-hydroxy-2-methyl-γ-pyrone) (0.05%), chrysin and a cyanogenic glycoside, gynocardin. Traces of the indole (β-carboline) alkaloids (e.g. harman, harmol, harmine) have been reported in the source plants; however, these alkaloids are undetectable in most commercial materials (*4–6, 8, 16*). The structures of the alkaloid harman and characteristic flavonoids are presented below.

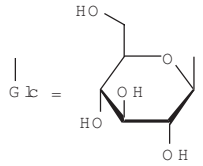
Medicinal uses

Uses supported by clinical data

None.

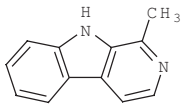


	R2	R6	R8
orientin	OH	H	Glc
iso-orientin	OH	Glc	H
lucenin-2	OH	Glc	Glc
schaftoside	H	Glc	Ara
isoschaftoside	H	Ara	Glc
vicenin-2	H	Glc	Glc
vitexin	H	H	Glc
isovitexin	H	Glc	H

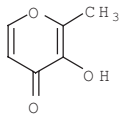


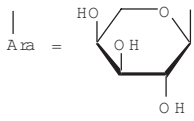
β-D-glucopyranosyl

harman



maltol





α-L-arabinopyranosyl

Uses described in pharmacopoeias and well established documents

Internally as a mild sedative for nervous restlessness, insomnia and anxiety. Treatment of gastrointestinal disorders of nervous origin (*1*, *5*, *11*).

Uses described in traditional medicine

As an anodyne, antispasmodic and mild stimulant (*1*, *6*). Treatment of dysmenorrhoea, neuralgia and nervous tachycardia (*1*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 5.0 g/kg body weight (bw) of a 60% ethanol extract of Herba Passiflorae per day for 3 weeks to rats did not reduce the pain response as measured in the tail-flick test using radiant heat, and no reductions in body temperature were observed (*17*). Intragastric administration of a 30% ethanol extract of the aerial parts reduced phenylbenzoquinone-induced writhing in mice, median effective dose 1.9 ml/kg bw (*18*).

Anti-inflammatory activity

Intragastric administration of 75.0–500.0 mg/kg bw of an ethanol extract of the aerial parts to rats reduced carrageenan-induced inflammation in the hind-paw model 60 minutes after administration (*19*). Intragastric administration of 500.0 mg/kg bw of the same extract to rats significantly reduced (16–20%; $P < 0.05$–0.001) the weight of granulomas induced by the implantation of cotton pellets (*19*).

Total leukocyte migration into the rat pleural cavity was reduced by approximately 40% in rats with induced pleurisy following intragastric administration of 500.0 mg/kg bw of an ethanol extract of the aerial parts. This effect was due to the suppression of polymorphonuclear and mononuclear leukocyte migration, and the effect was similar to that of 250.0 mg/kg bw of acetylsalicylic acid (*19*).

Antimicrobial activity

A 50% ethanol extract of up to 500.0 mg/ml of the aerial parts did not inhibit the growth of the following fungi: *Aspergillus fumigatus, Botrytis cinerea, Fusarium oxysporum, Penicillium digitatum, Rhizopus nigricans* and *Candida albicans* (*20*). A methanol extract of the aerial parts inhibited the growth of *Helicobacter pylori*, minimum inhibitory concentration 50.0 µg/ml (*21*).

Cardiovascular effects

In vitro perfusion of guinea-pig heart with a 30% ethanol extract of the aerial parts, 0.001%, increased the force of contraction of the heart muscle. Intravenous administration of 0.05 ml/kg bw of the extract had no effect on blood pressure in guinea-pigs or rats (*18*).

Central nervous system depressant activity

Intraperitoneal injection of 25.0 mg/kg bw of an aqueous extract of the aerial parts to mice reduced spontaneous locomotor activity and coordination. However, intraperitoneal administration of the same dose of a fluidextract to mice did not reduce motor activity (*22*). Intraperitoneal or intragastric administration of 60.0–250.0 mg/kg bw of a 30% ethanol or 40% ethanol extract to mice reduced spontaneous locomotor activity. Intragastric administration of 60.0 mg/kg bw of the 40% ethanol extract also potentiated pentobarbital-induced sleeping time, and intraperitoneal administration of 50 mg/kg bw significantly ($P < 0.05$) delayed the onset of pentylenetetrazole-induced seizures (*23*).

The effects of an aqueous or 30% ethanol extract of the aerial parts were assessed in mice using the unconditioned conflict test, the light/dark box choice procedure and the staircase test. The extracts were administered at doses of 100.0 mg/kg bw, 200.0 mg/kg bw, 400.0 mg/kg bw or 800.0 mg/kg bw, while control animals received normal saline. The aqueous extract reduced motor activity in the staircase and free exploratory tests, as measured by the number of rears, steps climbed or locomotor crossings following administration of the 400.0 mg/kg and 800.0 mg/kg doses. The aqueous extract also potentiated pentobarbital-induction of sleep. The 30% ethanol extract was not active in these tests, but appeared

to increase activity of the animals, having an anxiolytic effect at the 400.0 mg/kg dose (*24*).

Intraperitoneal administration of 160.0–250.0 mg/kg bw of an aqueous extract of the aerial parts to mice delayed pentylenetetrazole-induced convulsions, increased pentobarbital-induced sleeping time and reduced spontaneous motor activity (*25*).

Intragastric administration of a 30% ethanol extract of the aerial parts, corresponding to 5.0 g/kg bw, per day for 3 weeks to rats had no effect on body weight, rectal temperature, tail-flick or motor coordination. However, in a one-armed radial maze, the treated animals demonstrated a reduction in motor activity. No changes were observed in electroencephalographic parameters in the treated animals (*17*).

Intragastric administration of 800.0 mg/kg bw of a dried 30% ethanol extract of the aerial parts (containing 2.6% flavonoids) to mice did not affect locomotor activity, but did prolong hexobarbital-induced sleeping time (*26*).

Chrysin displayed high affinity for the benzodiazepine receptors in vitro, and reduced locomotor activity in mice following intraperitoneal administration of 30.0 mg/kg bw (*27, 28*). At the same dose, chrysin also increased pentobarbital-induced hypnosis (*28*).

Uterine stimulant effects

A fluidextract of the aerial parts, 1.0 mol/l, stimulated strong contractions in guinea-pig and rabbit uterus (not pregnant) in vitro (*22*). However, a fluidextract, 1.0–2.0 mol/l, did not stimulate contractions in the isolated uterus from pregnant guinea-pigs (*29*).

Toxicology

The oral median lethal dose of a 30% ethanol extract of the aerial parts in mice was 37.0 ml/kg bw (*18*). Toxicity in mice of an aqueous extract was observed only after intraperitoneal administration of 900.0 mg/kg bw (*25*). No acute toxicity was observed in mice given extracts of the aerial parts at doses of 500.0 mg/kg bw or 900.0 mg/kg bw (*25*, *30*).

Clinical pharmacology

No clinical data available for mono-preparations of Herba Passiflorae.

Adverse reactions

A single case of hypersensitivity with cutaneous vasculitis and urticaria following ingestion of tablets containing an extract of Herba Passiflorae was reported (*31*). In one case, use of the aerial parts was associated with IgE-mediated occupational asthma and rhinitis (*32*). A single case of se-

vere nausea, vomiting, drowsiness, prolonged QT segment and episodes of non-sustained ventricular tachycardia was reported in a female subject after self-administration of a therapeutic dose of the aerial parts (*33*). However, the clinical significance of this reaction has not been evaluated.

Contraindications

Herba Passiflorae has been shown to stimulate uterine contractions in animal models (*22*). Its use is therefore contraindicated during pregnancy.

Warnings

May cause drowsiness. The ability to drive a car or operate machinery may be impaired.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A fluidextract of Herba Passiflorae was not genotoxic at concentrations up to 1.3 mg/ml in *Aspergillus nidulans*, as assessed in a plate incorporation assay that permitted the detection of somatic segregation as a result of mitotic crossing-over, chromosome mal-segregation or clastogenic effects. No significant increase in the frequency of segregant sectors per colony were observed at any tested dose (*34*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of data concerning its safety and efficacy, Herba Passiflorae should not be used by nursing mothers without consulting a health-care practitioner.

Paediatric use

Owing to the lack of data concerning its safety and efficacy, Herba Passiflora should not be administered to children without consulting a health-care practitioner.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms

Powdered dried aerial parts, capsules, extracts, fluidextract and tinctures (*5*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Daily dose, adults: as a sedative: 0.5–2.0 g of aerial parts three to four times; 2.5 g of aerial parts as an infusion three to four times; 1.0–4.0 ml tincture (1:8) three to four times; other equivalent preparations accordingly (*2, 11*).

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Testa Plantaginis

Definition
Testa Plantaginis consists of the epidermis and collapsed adjacent layers removed from the seeds of *Plantago ovata* Forsk. (Plantaginaceae) (*1, 2*).

Synonyms
Plantago brunnea Morris, *P. decumbens* Forsk., *P. fastigiata* Morris, *P. gooddingii* Nelson et Kennedy, *P. insularis* Eastw., *P. ispaghula* Roxb. ex Flem., *P. lanata* Willd. ex Spreng., *P. leiocephala* Wallr., *P. microcephala* Poir., *P. minima* Cunn., *P. trichophylla* Nab., *P. villosa* Moench. (*3*).

Selected vernacular names
Ashwagolam, aspaghol, aspagol, bazarqutuna, blond psyllium, Blondes Psyllium, Ch'-Ch'ientzu, esfarzeh, esopgol, esparzeh, fisyllium, ghoda, grappicol, Indian plantago, Indische Psyllium, isabakolu, isabgol, isabgul, isabgul gola, isapagala-vittulu, ishppukol-virai, ispaghula, isphagol, vithai, issufgul, jiru, kabbéche, lokmet an naâja, obako, psyllium, plantain, spogel seed plantain (*3–5*).

Geographical distribution
Indigenous to Asia and the Mediterranean countries. Cultivated extensively in India and Pakistan; adapts to western Europe and subtropical regions (*6–8*).

Description
An annual, acaulescent herb. Stem highly ramified bearing linear leaves, which are lanceolate, dentate and pubescent. Flowers white and grouped into cylindrical spikes; sepals characterized by a distinct midrib extending from the base to the summit; petal lobes oval with a mucronate summit. Seeds oval, clearly carinate, 2–3 mm long, light grey-pink, with a brown line running along their convex side (*6*).

Plant material of interest: dried seed coats (epidermis)

General appearance

Pinkish-beige fragments or flakes up to 2 mm long and 1 mm wide, some showing a light brown spot corresponding to the location of the embryo before it was removed from the seed (*2*).

Organoleptic properties

Odour: weak, characteristic; taste: mucilaginous (*9*).

Microscopic characteristics

Particles angular, edges straight or curved and sometimes rolled. Composed of polygonal prismatic cells with four to six straight or slightly curved walls; cells vary in size in different parts of the seed coat, from about 25–60 µm long at the summit of the seed to 25–100 µm for the remainder of the epidermis, except at the edges of the seed, where the cells are smaller, about 45–70 µm (*3*).

Powdered plant material

Pale to medium buff-coloured, having a slight pinkish tinge and a weak characteristic odour. Entire or broken epidermal cells, which appear polygonal to slightly rounded in surface view and are filled with mucilage. Occasional single and compound (two to four components) starch granules, the individual grains being spheroidal plano- to angular-convex 2–25 µm in diameter, embedded in the mucilage. Mucilage stains red with ruthenium red and lead acetate TS. Also present, some elongated and rectangular cells from the lower part of epidermis, and radially swollen epidermal cells (*2*).

General identity tests

Macroscopic and microscopic examinations (*2*) and thin-layer chromatography for the presence of arabinose, xylose and galactose (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Complies with the test for foreign matter determined on 5.0 g of material (*2*).

Total ash
Not more than 4% (*2*).

Loss on drying
Not more than 12% (*2*).

Swelling index
Not less than 40 (*2*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements. *Plantago* products can be assayed for their fibre content by the Association of Official Analytical Chemists method (*13*).

Major chemical constituents
The major constituent is a mucilaginous hydrocolloid (20–30%), which is a soluble polysaccharide fraction composed primarily of an arabinoxylan (up to 85%). The polymer backbone is a xylan with 1→ 3 and 1→ 4 linkages with no apparent regularity in their distribution. The monosaccharides in this main chain are substituted on C-2 or C-3 by L-arabinose, D-xylose, and α-D-galacturonyl-(1→2)-L-rhamnose. Fixed oil (5–10%) is another major constituent (*5, 9, 14–16*).

Medicinal uses

Uses supported by clinical data

A bulk-forming laxative used therapeutically for restoring and maintaining bowel regularity (*15, 17–26*). Treatment of chronic constipation, temporary constipation due to illness or pregnancy, irritable bowel syndrome and constipation related to duodenal ulcer or diverticulitis (*18, 27*). Also indicated for stool softening in the case of haemorrhoids, or after anorectal surgery (*18, 20*). As a dietary supplement in the management of hypercholesterolaemia, to reduce the risk of coronary heart disease (*28*), and reduce the increase in blood sugar levels after eating (*24*).

Uses described in pharmacopoeias and well established documents

Short-term use for the symptomatic treatment of diarrhoea of various etiologies (*29–31*).

Uses described in traditional medicine

As an expectorant, antitussive and diuretic. Treatment of rheumatism, gout, glandular swelling and bronchitis (*5, 8*).

Pharmacology

Experimental pharmacology

Antidiarrhoeal activity

Intragastric administration of 0.4 g of Testa Plantaginis per day inhibited *Escherichia coli*-induced diarrhoea in pigs (*32*). Intragastric administration of the seed coats to calves, 18.89 g/l of oral rehydration solution, did not reduce the number or frequency of stools (*33*).

Antihypercholesterolaemic activity

Administration of the seed coats in the diet, 10%, to African green monkeys fed a high-cholesterol diet for 3.5 years significantly ($P < 0.05$) reduced plasma cholesterol levels by 39% and inhibited the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the liver and intestine (*34*). A further study in these animals also showed that this administration of the seed coats reduced plasma cholesterol concentrations by decreasing the synthesis of low-density lipoproteins (LDL) (*35*). Administration of the seed coats in the diet, 7.5%, to hamsters reduced cholesterol concentrations and increased sterol loss in the liver. The mechanism of action appears to involve a reduction of LDL cholesterol production and an increase in receptor-mediated LDL clearance (*36*). Administration of the seed coats, 7.5 g/100 g body weight (bw) daily to guinea-pigs fed a high-cholesterol diet significantly ($P < 0.0001$) reduced plas-

ma cholesterol levels by 39% as compared with controls (*37*). Alterations in hepatic cholesterol metabolism were observed in guinea-pigs after the administration of the seed coats (dose not specified). Treated animals fed a high fat and sucrose diet showed reductions in plasma LDL cholesterol, triacylglycerol, apolipoprotein B and hepatic cholesteryl ester concentrations, and a 45% increase in the number of hepatic apolipoprotein A/E receptors (*38*).

Administration of Testa Plantaginis in the diet, 5.0%, to rats reduced serum cholesterol concentrations (*39*). Administration of the seed coats in the diet, 10.0%, reduced total serum cholesterol concentrations and increased high-density lipoprotein (HDL) cholesterol in rats fed a high-cholesterol diet (*40*). Administration of the seed coats in the diet, 5.0%, to rats significantly ($P < 0.0001$) lowered an increase in serum cholesterol concentrations induced by feeding the animals trans-fatty acids (corn-oil margarine) (*41*).

Antihyperglycaemic activity

Administration of the seed coats in the diet, 2.5%, for 18 weeks to mice with genetically-induced diabetes reduced blood glucose levels and increased blood insulin concentrations (*42*).

Effects on bile acids

Administration of the seed coats in the diet, 5.0%, for 5 weeks to rats increased bile acid synthesis and lowered the hydrophobicity of the bile acid pool (*43*). Administration of the seed coat in the diet, 5.0%, to dogs fed a lithogenic diet for 6 weeks reduced the incidence of cholesterol gallstones by reducing the biliary cholesterol saturation index (*44*). Administration of the seed coats in the diet, 4.0–6.0%, for 5 weeks to hamsters fed a lithogenic diet increased faecal bile acid excretion by 400%, and reduced the concentration of taurine-conjugated bile acids in those receiving the highest dose. In addition, the treatment normalized the lithogenic index and prevented cholesterol gallstone formation as compared with controls (*45*). Administration of the seed coats in the diet, 8.0%, for 5 weeks to hamsters increased daily faecal neutral sterol excretion by 90% owing to higher faecal output. Daily faecal bile acid excretion and total faecal bile acid concentrations were also increased (*46*).

Gastrointestinal effects

Administration of the seed coats in the diet, 10.0–20.0%, for 4 weeks to rats resulted in increased levels of gastric, intestinal and colonic mucin, and increased faecal weight compared with control animals (*47*). In vitro,

a 70% methanol extract of the seed coats, 6.0 mg/ml, stimulated contractions of isolated guinea-pig ileum (*48*).

Clinical pharmacology

Antidiarrhoeal activity

In patients with acute and chronic diarrhoea, 10 g of Testa Plantaginis per day for 7 days increased the viscosity of the intestinal contents, owing to the binding of fluid by the seed coats, thereby decreasing the frequency of defecation (*29, 30*).

In a placebo-controlled trial, 10 female patients with diarrhoea-predominant irritable bowel syndrome were treated with 3.4 g of the seed coats three times per day for 4 weeks after an initial 4-week baseline placebo period. The treatment significantly improved patient global satisfaction with bowel function ($P < 0.02$), and urge to defecate ($P < 0.01$) compared with placebo. Treatment also reduced movement frequency and doubled stool viscosity (*31*).

Eight subjects participated in a randomized, placebo-controlled cross-over study on the moderation of lactulose-induced diarrhoea in irritable bowel syndrome. Gastric emptying and small bowel and colonic transit were measured following consumption of 20 ml of lactulose three times per day with or without 3.5 g of Testa Plantaginis three times per day. The seed coats significantly delayed gastric emptying by 50% ($P < 0.05$); small bowel transit was unchanged, and progression through the colon was delayed. It was concluded that the seed coats probably delayed gastric emptying by increasing meal viscosity, and reduced the acceleration of colon transit by delaying the production of gaseous fermentation products (*49*).

Antihypercholesterolaemic activity

Numerous clinical investigations with the seed coats have demonstrated a reduction in serum cholesterol levels in patients with mild to moderate hypercholesterolaemia (*23, 26*). A meta-analysis assessed the hypolipidaemic effects and safety of the seed coats when used as an adjunct to a low-fat diet in men and women with hypercholesterolaemia. Eight clinical trials met the criteria for the meta-analysis and included a total of 384 and 272 subjects receiving the seed coats or cellulose placebo, respectively. All of the trials evaluated the hypocholesterolaemic effects of 10.2 g of the seed coats daily together with a low-fat diet for ≥ 8 weeks. Consumption of seed coats significantly lowered serum total cholesterol by 4% ($P < 0.0001$), LDL cholesterol by 7% ($P < 0.0001$), and the ratio of apolipoprotein B to apolipoprotein A-I by 6% ($P < 0.05$) compared with pla-

cebo. No effects on serum HDL or triacylglycerol concentrations were observed (*26*).

Another meta-analysis assessed the efficacy of the consumption of a cereal product enriched with the seed coats in reducing blood total, LDL and HDL cholesterol levels in 404 adults with mild to moderate hypercholesterolaemia, who were also consuming a low-fat diet. Studies were considered to be eligible for inclusion in the meta-analysis if they were randomized controlled trials, and included a control group that ate cereal containing at least 3.0 g of soluble fibre daily. Eight published and four unpublished studies, conducted in four countries, met the criteria. The results of the meta-analysis demonstrated that subjects who consumed cereals containing the seed coats had lower total and LDL cholesterol concentrations, with differences of 5% and 9%, respectively, than subjects who ate a control cereal; HDL cholesterol concentrations were unaffected. The analysis indicates that consumption of cereals enriched with the seed coats as part of a low fat diet improves the blood lipid profile in hypercholesterolaemic adults to a greater extent than the low-fat diet alone (*23*).

A multicentre clinical investigation assessed the long-term effectiveness of Testa Plantaginis fibre as an adjunct to diet in the treatment of primary hypercholesterolaemia. Subjects were required to follow an American Heart Association Step I diet for 8 weeks (dietary adaptation phase). Eligible subjects with serum LDL-cholesterol concentrations of 3.36–4.91 mmol/l were then randomly assigned to receive 5.1 g of the seed coats or a cellulose placebo twice per day for 26 weeks in conjunction with diet therapy. The results demonstrated that serum total and LDL cholesterol concentrations were 4.7% and 6.7% lower, respectively, in the treatment group than in the placebo group after 24–26 weeks ($P < 0.001$) (*25*). A multicentre, double-blind, placebo-controlled, randomized trial assessed the cholesterol-level-lowering effect of the seed coats with dietary advice compared with placebo and dietary advice in 340 patients with mild-to-moderate hypercholesterolaemia. An initial 8-week diet-only period was followed by a 2-week treatment period. Treatment with 7.0 g or 10.5 g of the seed coats per day was continued for a further 12 weeks in some patients. Levels of total, LDL and HDL cholesterol, triglycerides and apolipoproteins A1 and B were measured. Treatment with the seed coats at both doses produced significantly greater reductions in LDL cholesterol levels than did placebo ($P = 0.009$ and $P < 0.001$). The seed coats plus modification of diet reduced LDL cholesterol levels by 10.6–13.2% and total cholesterol levels by 7.7–8.9% during the 6-month period (*50*).

A randomized controlled clinical trial assessed the effects of the seed coats as an adjunct to a traditional diet for diabetes in the treatment of 34 subjects with type 2 diabetes and mild-to-moderate hypercholesterolaemia. After a 2-week dietary stabilization phase, subjects were randomly assigned to receive 5.1 g of the seed coats or cellulose placebo twice per day for 8 weeks. The group treated with the seed coats showed significant improvements in glucose and lipid values as compared with the placebo group. Serum total and LDL-cholesterol concentrations were 8.9% ($P < 0.05$) and 13.0% ($P = 0.07$) lower, respectively, than in the placebo group. All-day and post-lunch postprandial glucose concentrations were 11.0% ($P < 0.05$) and 19.2% ($P < 0.01$) lower in the treated group (*24*).

In a clinical trial, the diet of six normal and five ileostomy subjects was supplemented with 10.0 g of the seed coats per day for 3 weeks, while six normal and four ileostomy subjects received 10.0 g of *Plantago ovata* seeds per day. Faecal and ileostomy output, sterol excretion, serum cholesterol and triglycerides were measured before and after supplementation. The seed coats had no effect on cholesterol or triglyceride concentrations in either normal or ileostomy subjects. Total and HDL cholesterol concentrations were reduced on average by 6.4% and 9.3%, respectively, in the normal group after seed supplementation. No effect on faecal bile acid excretion in the normal subjects was found in either group. Ileostomy bile acids were increased (on average 25%) after seed supplementation, whereas no effect on cholesterol concentrations was found. These results suggest that the seeds might be more effective than the seed coats in reducing serum cholesterol, that this cholesterol-lowering effect is not mediated by increased faecal bile acid losses, and that increased ileal losses of bile acids might be compensated for by enhanced reabsorption in the colon (*51*).

In a double-blind, placebo-controlled study involving 26 men, supplementation of the diet with 3.4 g of the seed coats three times per day for 8 weeks produced a decrease in serum cholesterol (-14.8%) and LDL cholesterol (-20.2%) (*52*). In a similar study, in which the seed coats were added to a low-fat diet, improvements in cholesterol parameters were observed after 8 weeks of therapy (*53*). The reduction in serum cholesterol may be due to increased excretion of bile acids in the faeces, which in turn stimulates synthesis of new bile acids from cholesterol (*22, 54*).

In a clinical study to assess the effect of the seed coats on faecal bile acid weights and concentrations, 16 healthy adults consumed 7.0 g of the seed coats per day for the middle 8 weeks of a 12-week period. Stool samples were collected and analysed for faecal bile acid content, and their form and dry weight were determined. Administration of the seed coats

significantly ($P < 0.01$) lowered faecal lithocholic and isolithocholic acids and the weighted ratio of lithocholic acids to deoxycholic acid. The change in the faecal bile acid profile indicates a reduction in the hydrophobicity of the bile acids in the enterohepatic circulation (*55*).

Laxative activity

Administration of the seed coats, solubilized in water, increases the volume of the faeces by absorbing fluids in the gastrointestinal tract, thereby stimulating peristalsis (*56*). The seed coats also reduce intraluminal pressure, increase colon transit time, and increase the frequency of defecation (*18, 20, 57*). Soluble fibres, such as those contained in the seed coats, are rapidly metabolized by colonic bacteria to volatile fatty acids, which are then absorbed by the colon, and increase the production of colonic mucin.

The therapeutic efficacy of the seed coats is due to the swelling of the mucilaginous fibre when mixed with water, which gives bulk and lubrication (*22*). The seed coats increase stool weight and water content owing to the water-bound fibre residue, and an increased faecal bacterial mass (*18, 20*). Clinical studies have demonstrated that ingestion of 18.0 g of the seed coats increases faecal fresh and dry weights as compared with placebo (*15*).

The digestibility of the seed coats and their faecal bulking effect were studied in seven healthy volunteers who ingested a low-fibre diet plus either placebo or the seed coats, 18 g/day, during two 15-day periods. There were no differences between the groups in whole gut transit time and gas excretion in breath and flatus. Faecal wet and dry weights rose significantly ($P = 0.009$ and $P = 0.037$, respectively) in the treated subjects. Faecal short-chain fatty acid concentrations and the molar proportions of propionic and acetic acids also increased in the treated group (*15*).

Adverse reactions

Sudden increases in dietary fibre may cause temporary gas and bloating. These side-effects may be reduced by a gradual increase of fibre intake, starting at one dose per day and gradually increasing to three doses per day (*58*). Occasional flatulence and bloating can be reduced by decreasing the amount of the seed coats taken for a few days (*58*).

Allergic reactions to ingestion or inhalation of *Plantago* products have been reported, especially after previous occupational exposure to these products (*59–64*). These reactions range from urticarial rashes to anaphylactic reactions (rare) (*60, 65*). One rare case of fatal bronchospasm has been reported in a Testa Plantaginis-sensitive patient with asthma (*62*).

Contraindications

Testa Plantaginis should not be used by patients with faecal impaction, undiagnosed abdominal symptoms, abdominal pain, nausea or vomiting unless advised by their health-care provider. Testa Plantaginis is also contraindicated following any sudden change in bowel habits that persists for more than 2 weeks, in rectal bleeding or failure to defecate following use of a laxative, and in patients with constrictions of the gastrointestinal tract, potential or existing intestinal blockage, megacolon, diabetes mellitus that is difficult to regulate, or known hypersensitivity to the seed coats (*14, 22*).

Warnings

To minimize the potential for allergic reaction, health professionals who frequently dispense powdered products prepared from Testa Plantaginis should avoid inhaling airborne dust while handling these products. To prevent generating airborne dust, the product should be spooned from the packet directly into a container and then the liquid should be added (*58*).

Testa Plantaginis products should always be taken with sufficient amounts of liquid, e.g. 5.0 g of the seed coats with 150 ml of liquid. Failure to do so may result in swelling of the seed coats and blockage of the oesophagus, which may cause choking. Intestinal obstruction may occur if an adequate fluid intake is not maintained. The seed coats should not be used by those with difficulty in swallowing or throat problems. Anyone experiencing chest pain, vomiting or difficulty in swallowing or breathing after taking Testa Plantaginis should seek immediate medical attention. Treatment of the elderly and the debilitated requires medical supervision.

Testa Plantaginis should be taken at least 2 h before or after other medications to prevent delayed absorption of other drugs (*66*). If bleeding, or no response and abdominal pain occur 48 h after ingesting the seed coats, treatment should be discontinued and medical advice sought (*58*).

Precautions

General

Testa Plantaginis should be taken with adequate volumes of fluid. Products should never be taken orally in dried powder form owing to possibility of causing bowel or oesophageal obstruction. In patients confined to bed or undertaking little physical exercise, a medical examination may be necessary prior to treatment with the seed coats.

Drug interactions

Bulking agents may diminish the absorption of some minerals (calcium, magnesium, copper and zinc), vitamins (B_{12}), cardiac glycosides and coumarin derivatives (*3, 52, 67–68*). However, more recent studies suggest that since seed coats do not contain phytates, they will not bind to vitamins and minerals and are therefore no cause for concern (*69–71*). The co-administration of the seed coats with lithium salts may reduce plasma concentrations of the latter and inhibit their absorption from the gastrointestinal tract (*72*). The seed coats may also decrease the rate and extent of carbamazepine absorption, and induce subclinical levels of the drug. Ingestion of lithium salts or carbamazepine and the seed coats should therefore be separated by as long an interval as possible (*73*). Ingestion of the seed coats 2 hours before or after the administration of other drugs is suggested (*66*). Individual monitoring of the plasma levels of these drugs, especially in patients also taking products containing Testa Plantaginis is also recommended. Insulin-dependent diabetics may require less insulin (*14*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried seed coats available commercially as chewable tablets, granules, wafers and powder. Store in a well closed container, in a cool dry place, protected from light (*2, 19*).

Posology

No information available.

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Radix Rehmanniae

Definition

Radix Rehmanniae consists of the dried roots and rhizomes of *Rehmannia glutinosa* Libosch. or *Rehmannia glutinosa* Libosch. var. *purpurea* Makino (Scrophulariaceae) (*1–4*).[1]

Synonyms

Digitalis glutinosa Gaertn., *Gerardia glutinosa* Bunge, *Rehmannia chinensis* Libosch., *R. sinensis* (Buc'hoz) Libosch. ex Fisch. et C.A. Mey. (*5*).

Selected vernacular names

Akayajio, di-huang, cû sinh dja, dihuang, dihuáng, dja hoâng, figwort, ji-whang, rehmannia, sheng dihuang, sheng-ti-pien, shu di, sin dja, ti huang (*4–7*).

Geographical distribution

Indigenous to China. Cultivated in China, Japan and Republic of Korea (*6, 8*).

Description

A perennial herb 10–40 cm high, with a thick, orange tuberous root, about 3–6 cm in diameter. Basal leaves fasciculate, obovate or long elliptic, 3–10 cm long, 1.5–2.0 cm wide; apex obtuse; tapering to a short petiole, coarsely dentate, pubescent, the underside often reddish. Flowers are solitary, borne in leaf axils; calyx five-lobed, upper lobes longest; corolla obliquely funnel form, slightly swollen on lower side, about 4 cm long, dull purple-brown and creamy yellow, densely glandular-pubescent, two-lipped; upper lobes shorter than the three lower lobes; tube with two ridges extending inside from sinuses of lower lip; four stamens borne near

[1] In the *Pharmacopoeia of the People's Republic of China* (*4*), fresh plant material is also permitted. In *The Japanese Pharmacopoeia* (*2*), steam-treated root material is also permitted.

base of corolla, anthers not coherent, disc ring-like, poorly developed; ovary superior, stigma two-lobed. Fruits are capsules (*6, 8*).

Plant material of interest: dried roots and rhizomes

General appearance

Fusiform root, 5–12 cm long, 1–6 cm in diameter, often broken or markedly deformed in shape. Externally, yellow-brown to blackish brown, with deep, longitudinal wrinkles and constrictions. Texture soft and tenacious, not easily broken. In transverse section yellow-brown to blackish brown, and cortex darker than xylem in colour. Pith hardly observable (*1, 2, 4*).

Organoleptic properties

Odour: characteristic; taste: slightly sweet, followed by a slight bitterness (*1, 2, 4*).

Microscopic characteristics

Transverse sections of the root show 7–15 layers of cork cells. Cortex parenchyma cells loosely arranged. Outer region of cortex composed of scattered secretory cells containing orange-yellow oil droplets. Stone cells occasionally found. Phloem relatively broad. Cambium is in a ring. Xylem rays broad, vessels sparse and arranged radially (*1, 2, 4*).

Powdered plant material

Dark brown. Cork cells brownish, subrectangular in lateral view, regularly arranged. Parenchyma cells subrounded, containing subrounded nuclei. Secretory cells similar to ordinary parenchyma cells in shape, containing orange or orange-red oil droplets. Border pitted and reticulated vessels up to about 92 µm in diameter (*3, 4*).

General identity tests

Macroscopic and microscopic examinations (*1–4*), and thin-layer chromatography (*3, 4*). A high-performance liquid chromatography method for catalpol, the major iridoid monoterpene, is available (*9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Total ash
Not more than 6% (*1*, *2*, *4*).

Acid-insoluble ash
Not more than 2.5% (*1*, *2*).

Water-soluble extractive
Not less than 65% (*3*, *4*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

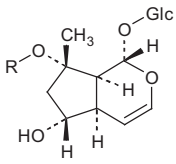
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter, sulfated ash, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

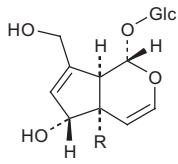
Chemical assays
To be established in accordance with national requirements.

Major chemical constituents
The major constituents are iridoid monoterpenes (2.6–4.8%) (*13*) including catalpol, ajugol, aucubin, rehmanniosides A–D, monomelittoside, melittoside, verbascoside, jionosides A1, A2, B1, B2, C, D and E (*5*, *7*, *14*, *15*). In addition, immunomodulating polysaccharides have also been reported (*16–18*). Representative structures of the iridoid monoterpenes are presented below.



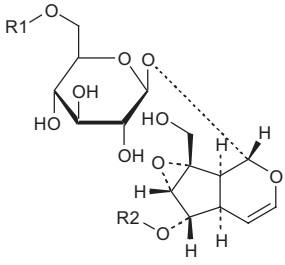
ajugol R = H

rehmannioside C R = Gal

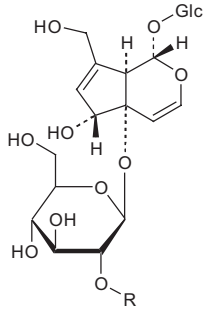


aucubin R = H

monomelittoside R = OH

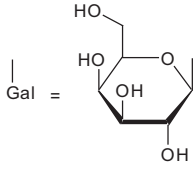


	R1	R2
catalpol	H	H
rehmannioside A	Gal	H
rehmannioside B	H	Gal

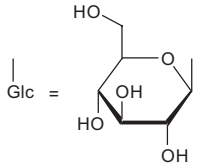


melittoside R = H

rehmannioside D R = Glc



β-D-galactopyranosyl



β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

None. Although published case reports indicate that Radix Rehmanniae is used for the treatment of rheumatoid arthritis and hypertension (*19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Internally for the symptomatic treatment of fevers, diabetes, hypertension, skin eruptions and maculation, sore throat, hypermenorrhoea and polymenorrhoea (*4, 20*). As a tonic to stimulate the immune system (*21*).

Uses described in traditional medicine

As an antispasmodic, diuretic and emmenagogue. Treatment of burns, diarrhoea, dysentery, metrorrhagia and impotence (*7, 20, 22, 23*).

Pharmacology

Experimental pharmacology

Antibacterial activity

A hot aqueous extract of Radix Rehmanniae (concentration not specified) did not inhibit the growth of *Staphylococcus aureus* or *Escherichia coli* in vitro (*24*).

Antidiarrhoeal activity

Intragastric administration of 2.0 g/kg body weight (bw) of an aqueous extract of the roots had no effects on serotonin-induced diarrhoea in mice (*25*).

Antihepatotoxic activity

A decoction of the roots, 25.0 µl/ml, inhibited hepatitis antigen expression in cultured hepatocytes infected with hepatitis B virus (*26*). An 80% methanol extract of the roots, 1.0 mg/ml, significantly inhibited ($P < 0.05$) the release of lactate dehydrogenase, glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) induced by carbon tetrachloride treatments in rat hepatocytes (*27*).

Intraperitoneal administration of 500.0 mg/kg bw of a methanol extract of roots to rats inhibited the increase in blood alkaline phosphatase, GOT and GPT activities caused by hepatotoxicity induced by α-naphthyl-isothiocyanate or carbon tetrachloride (*28, 29*).

Antihyperglycaemic activity

Intragastric administration of an aqueous or methanol extract of the roots, 200.0 mg/kg bw or 111.5 mg/kg bw, to rats decreased streptozocin-induced hyperglycaemia (*30*). However, no such effects were observed in diabetic rats treated orally with 1.6–2.0 g/kg bw of a hot aqueous extract or a decoction of the roots daily for 8 days. These data suggest that the chemical constituents responsible for the activity may be heat sensitive (*31–33*).

Intraperitoneal administration of 100.0 mg/kg bw of a polysaccharide-enriched extract of the roots to mice decreased streptozocin-induced hyperglycaemia, reduced the activities of glucose-6-phosphatase and phosphofructokinase, stimulated the activities of glucose-6-phosphate dehydrogenase and hexokinase, and stimulated insulin release from the pancreas (*34*).

Anti-inflammatory activity

Intragastric administration of 200.0 mg/kg bw of a 50% ethanol extract of the roots to rats did not inhibit carrageenan-induced footpad oedema or adjuvant-induced arthritis (*35*).

Antitumour activity
After 24 h of treatment with polysaccharides isolated from the roots, 0.1 mg/ml, p53 gene expression in Lewis lung cancer cells increased almost four-fold (*36*). Intraperitoneal administration of 20.0 mg/kg bw or 40.0 mg/kg bw of polysaccharides isolated from the roots to mice increased the expression of the proto-oncogene c-fos by ~50% and decreased the expression of c-myc by ~ 30% compared with administration of saline (*37*). Intraperitoneal administration of 20.0–40.0 mg/kg bw of a polysaccharide isolated from the roots daily for 8 days after the second day of tumour transplantation inhibited the growth of solid tumours S180, Lewis B16, and H22 in mice. Oral treatment was only effective against S180. Treatment also enhanced the proliferation of splenic T lymphocytes and blocked the inhibition of natural killer cell activity caused by tumour cell growth (*16*).

Antiulcer activity
Intragastric administration of 6.0 g/kg bw of an aqueous extract of the roots to rats reduced absolute ethanol-induced gastric mucosal damage by 74.7%. The protective effects of the extract were reduced when the animals were pretreated with a decoction of chilli fruits (40–80%), suggesting that they were mediated by capsaicin-sensitive neurons in the gastric mucosa (*38*).

Central nervous system depressant effects
Intragastric administration of 2.5 g/kg bw of an aqueous extract of the roots prolonged pentobarbital-induced sleeping time in mice with stressor yohimbine-induced sleep deprivation (*39*).

Enzyme-inhibiting effects
A petroleum ether extract of the roots inhibited the activity of aldose reductase, median inhibitory concentration (MIC) 8.5 µg/ml (*40*). An aqueous extract of the roots (concentration not specified) inhibited the activity of angiotensin II (*41*). A decoction of the roots inhibited the activity of a sodium/potassium adenosine triphosphatase isolated from horse kidney, MIC 5.76 mg/ml. A 95% ethanol extract of the roots was not active in this assay (*42*).

Haematological effects
Intragastric administration of 10.0–20.0 mg/kg bw of an oligosaccharide fraction isolated from the roots daily for 8 days to senescence-accelerated mice enhanced DNA synthesis in bone marrow cells, increased the number of granulocyte/macrophage progenitors, and increased early-

and late-differentiated erythrocyte progenitors (*43*). Intragastric administration of (10.0–20.0 mg/kg bw of an oligosaccharide fraction isolated from the roots to senescence-accelerated mice enhanced the proliferation of hematopoietic stem cells, and increased the number of colony-forming-unit granulocytes/macrophages, colony-forming- and burst-forming-unit erythroid cells, and the concentration of peripheral leukocytes (*44*). Intragastric administration of a decoction of the roots (dose not specified) to mice inhibited blood clotting induced by acetylsalicylic acid (*45*). A 50% ethanol extract of the roots increased erythrocyte deformability and erythrocyte ATP concentrations, and inhibited polybrene-induced erythrocyte aggregation and the activity of the fibrinolytic system (*46*). Intragastric administration of 200.0 mg/kg bw of a 50% extract of the roots to rats inhibited the reduction of fibrinolytic activity and erythrocyte deformability, decrease in erythrocyte counts, and increase in connective tissue in the thoracic artery in arthritis induced by chronic inflammatory adjuvant (*35*). Intragastric administration of a 50% ethanol extract of the roots (dose not specified) to rats increased blood flow in the dorsal skin, abdominal vein and spleen tissue (*47*).

Immunological effects

Intraperitoneal administration of 10.0 mg/kg bw or 20.0 mg/kg bw of a polysaccharide extract isolated from the roots to mice bearing sarcoma 180 tumours increased cytotoxic T-lymphocyte activity on day 9 after administration, but did not significantly change interleukin-2 concentrations (*48*). In another study, administration of the same polysaccharide at the same dose to mice with the same tumour prevented the suppression of cytotoxic T lymphocyte activity and interleukin 2 secretion caused by excessive tumour growth (*49*). Intraperitoneal administration of 0.1 mg/kg bw of an aqueous extract of the roots to mice 1 hour prior to treatment with compound 48/80 inhibited compound 48/80-induced fatal shock by 53.3% and reduced plasma histamine release (*21*). In rat peritoneal mast cells, the same extract, 1.0 mg/ml, significantly ($P < 0.05$) inhibited anti-dinitrophenol IgE-induced histamine release and tumour necrosis factor-α production (*21*).

Intragastric administration of 100.0 mg/kg bw of jionoside B and verbascoside isolated from the roots to mice produced a 36% and 18% suppression of haemolytic plaque-forming cells in the spleen, respectively, compared with a 52.5% suppression following the administration of cyclophosphamide (*50*).

Platelet aggregation inhibition

Aqueous, hexane and methanol extracts of the roots, 1.0%, inhibited platelet aggregation induced by adenosine diphosphate, arachidonic acid and collagen in isolated rat platelets (*51*).

Toxicology

Intragastric administration of 60.0 g/kg bw of a decoction of the roots per day for 3 days to mice produced no adverse effects or death of the animals (*19*). Intragastric administration of 18.0 g/kg bw of a decoction of the roots per day for 45 days to rats produced no change in body weight or liver enzymes (*19*). Intragastric administration of 600.0 mg/kg bw of a 90% methanol extract of the roots per day for 4 days to mice had no toxic effects and did not induce weight loss (*52*). Intragastric administration of 400.0 mg/kg bw of a 90% methanol extract of the roots per day for 4 days to mice inhibited DNA synthesis in the bone marrow (*52*). The median oral lethal dose of a 70% methanol extract of the roots in mice was >2.0 g/kg (*53*).

Clinical pharmacology

Treatment of 23 cases of arthritis with a decoction of the roots (dose not specified) improved symptoms in most patients. Patients reported a decrease in joint pain, a reduction in swelling and improvements in joint movement. In addition, a normalization of the erythrocyte sedimentation rate was observed (*19*).

A decoction of the roots, corresponding to 30.0–50.0 g of roots, administered daily for 2 weeks to 62 patients with hypertension reduced blood pressure, serum cholesterol and triglycerides, and improved cerebral blood flow and the electrocardiogram (no further details available) (*19*).

Adverse reactions

Diarrhoea, abdominal pain, oedema, fatigue, vertigo and heart palpitations have been reported. However, these adverse effects were transient and disappeared within several days (*19, 54*).

Contraindications

Radix Rehmanniae is contraindicated in chronic liver or gastrointestinal diseases and in patients with diarrhoea (*3*). Owing to its potential antiimplantation effects (*55*), the use of Radix Rehmanniae during pregnancy is also contraindicated.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of Radix Rehmanniae, 40.0–50.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98, and TA100 (*56, 57*). However, intraperitoneal administration of 4.0 mg/kg bw of the aqueous extract to mice, equal to 10–40 times the amount used in humans, was mutagenic (*57*). Intraperitoneal administration of a hot aqueous extract of the roots (dose not specified) to mice did not enhance cyclophosphamide-induced chromosomal damage (*58*). Subcutaneous administration of a hot aqueous extract of the roots (dose not specified) inhibited embryonic implantation in treated female mice (*55*). No effects were observed after in vitro treatment of human sperm with an aqueous extract of the roots, 100.0 mg/ml (*59*).

Pregnancy: teratogenic effects

No teratogenic or abortifacient effects were observed in rats following intragastric administration of 500.0 mg/kg bw of a 70% methanol extract of the roots starting on the 13th day of pregnancy (*53*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to a lack of data on the safety and efficacy of Radix Rehmanniae, its use by nursing mothers is not recommended without supervision by a health-care provider.

Paediatric use

Owing to a lack of data on the safety and efficacy of Radix Rehmanniae, its use in children is not recommended without supervision by a health-care provider.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms

Dried roots and rhizomes for infusions and decoctions. Store in a well-closed container in a cool, dry place, protected from light (*4*).

Posology

(Unless otherwise indicated)
Daily dose: 9–15 g of dried roots and rhizomes as an infusion or decoction (*4*).

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Fructus Schisandrae

Definition

Fructus Schisandrae consists of the dried ripe fruits of *Schisandra chinensis* (Turcz.) Baill. (Schisandraceae) (*1–3*).[1]

Synonyms

Idesia polycarpa Morr. et de Vos, *Kadsura chinensis* Turcz., *Maximowiczia amurensis* Rupr., *M. chinensis* Rupr., *M. sinensis* Rupr., *Maximowitschia japonica* A. Gray, *Polycarpa maximowiczii* Morr. et de Vos, *Schisandra chinensis* var. *typica* Nakai, *Schizandra japonica* Sieb. et Zucc., *Sphaerostemma japonicum* A. Gray (*4*).

Selected vernacular names

Bac ngu vi tu, bei wuweizi, Chinesischer Limonenbaum, Chinese magnolia vine, Chinese mock-barberry, chosen-gomishi, lemonwood, limonnik kitajskij, matsbouza, m mei gee, ngu mei gee, northern magnoliavine, o-mee-ja, o-mi-d'ja, o-mi-ja, omicha, ornija, pen ts'ao, schisandra, dheng-mai-yin, wu-wei-zi, wu-weitzu (*4–8*).

Geographical distribution

Indigenous to Russia (Primorsk and Khabarovsk regions, the Kuril islands, southern Sakhalin) north-eastern China, Japan and the Korean peninsula. Cultivated in China and Republic of Korea (*7, 9*).

Description

A deciduous woody climbing vine, up to 8 m long. Leaves alternate, petiolate, ovate or oblong-obovoid, 5–11 cm long, 2–7 cm wide, apex acute or acuminate; base cuneate or broadly cuneate, membranous. Flowers uni-

[1] The *Pharmacopoeia of the People's Republic of China (3)* also recognizes the fruits of *Schisandra sphenanthera* Rehd. et Wils.

sexual, dioecious, solitary or clustered axillary, yellowish-white to pinkish; male flower stalked, with five stamens, filaments united into a short column; female flower has numerous carpels. Fruits, 5–8 mm in diameter, arranged into a long spike with globular, deep-red berries. Seeds, one to two per berry, reniform, shiny, smooth, yellowish brown, 4.5 mm long, 3.5 mm in diameter (*5, 7, 9, 10*).

Plant material of interest: dried ripe fruits

General appearance

Irregularly spheroidal or compressed-spheroidal, 5–8 mm in diameter. Externally dark red to blackish-red or covered with "white powder", wrinkled, oily, with soft pulp. Seeds, one to two, reniform, externally brownish-yellow to dark red-brown, lustrous, with distinct raphe on the dorsal side; testa thin and fragile (*1, 3*).

Organoleptic properties

Odour of pulp: slight; odour of seed: aromatic on crushing; taste of pulp: sour; taste of seed: pungent and slightly bitter (*1, 3*).

Microscopic characteristics

Pericarp with one layer of square or rectangular epidermal cells, walls relatively thickened, covered with cuticle, oil cells scattered. Mesocarp with 10 or more layers of parenchymatous cells containing starch grains, scattered with small collateral vascular bundles. Endocarp with one layer of parenchymatous cells. Outermost layer of testa consists of radially elongated stone cells, thick walled, with fine and close pits and pit canals; then several lower layers of stone cells, subrounded, triangular or polygonal with larger pits, and a few layers of parenchymatous cells and raphe, with vascular bundles. Endosperm cells contain yellowish-brown coloured oil droplets and aleurone grains (*3*).

Powdered plant material

Dark purple in colour. Stone cells of epidermis of testa polygonal or elongated-polygonal in surface view, 18–50 µm in diameter, wall thickened with very fine and close pit canals, lumina containing dark brown contents. Stone cells of the inner layer of the testa polygonal, subrounded or irregular, up to 83 µm in diameter, walls slightly thickened, with relatively large pits. Epidermal cells of the pericarp polygonal in surface view, anticlinal walls slightly beaded, with cuticle striations, scattered with oil cells. Mesocarp cells shrivelled, with dark brown contents and starch granules (*3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), and thin-layer chromatography for the presence of deoxyschizandrin (schisandrin A) (*2, 3, 7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Foreign organic matter

Not more than 1.0% (*1, 3*).

Total ash

Not more than 5.0% (*1, 2*).

Acid-insoluble ash

Not more than 1.0% (*2*).

Water-soluble extractive

Not less than 35% (*2*).

Alcohol-soluble extractive

Not less than 40% (*2*).

Moisture

Not more than 8.0% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia* (*12*) and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Other purity tests

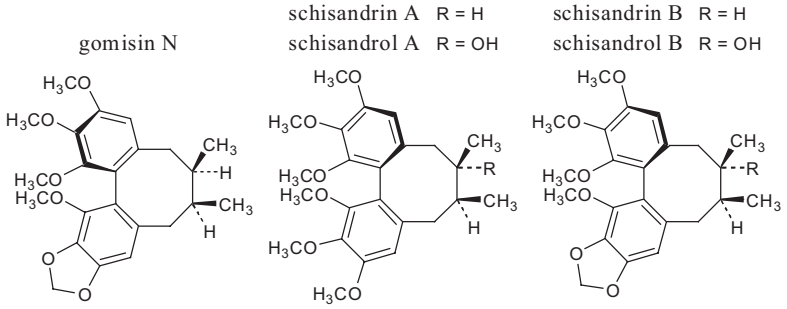
Chemical tests to be determined in accordance with national requirements.

Chemical assays

Contains not less than 0.4% schizandrin (schisandrin, schisandrol A, wuweizichun A) determined by high-performance liquid chromatography (*3*). Additional high-performance liquid chromatography and high-performance liquid chromatography–mass spectrometry methods are available (*14, 15*).

Major chemical constituents

The major constituents are lignans of biological interest with the dibenzo[*a,c*]cyclooctadiene skeleton. Among the approximately 30 lignans are schizandrin (schisandrin, schisandrol A, wuweizichun A, 0.2–0.7%), gomisin A (schisandrol B, wuweizichun B, wuweizi alcohol B, 0.1–3.0%), deoxyschizandrin (deoxyschisandrin, schisandrin A, wuweizisu A, 0.1–9.0%), (±)-γ-schizandrin (schisandrin B, γ-schisandrin B, wuweizisu B, 0.1–5.0%), and gomisin N (pseudo-γ-schisandrin B, 0.1–0.5%) (*7, 8*). The structures of schizandrin, deoxyschizandrin, gomisin N, gomisin A and (±)-γ-schizandrin are presented below:



Medicinal uses

Uses supported by clinical data

None. Although some clinical evidence supports the use of Fructus Schisandrae for the treatment of psychosis, gastritis, hepatitis and fatigue (*16, 17*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Treatment of chronic cough and asthma, diabetes, urinary tract disorders. As a general tonic for treating fatigue associated with illness (*3, 7, 9, 16*).

Uses described in traditional medicine

As an astringent, antitussive, antidiarrhoeal, expectorant and sedative (*8*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

External application of gomisin A (schisandrol B), 0.6 mg/ear, inhibited inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in mice. External application of gomisin J and schisandrin C also inhibited the inflammation induced by TPA in mice. The median effective dose (ED_{50}) of these compounds ranged between 1.4 µmol and 4.4 µmol, with gomisin A having the strongest anti-inflammatory effect (*18*).

Antihepatotoxic activities

In vivo studies have demonstrated that the fruits have liver-protectant effects. Intragastric administration of 80.0 mg/kg bw of a lignan-enriched extract of the fruits to rats prevented hepatotoxicity induced by carbon tetrachloride, prevented glutathione depletion and stimulated the activity of glutathione reductase (*19, 20*). In experimental models, the activity of serum glutamic pyruvic transaminase (SGPT) induced by the administration of carbon tetrachloride or paracetamol in mice, thioacetamide in rats, and ethinyl estradiol 3-cyclopentylether in rabbits was reduced by oral administration of 1.0–10.0 g/kg bw of a 95% ethanol extract of fruits (*21, 22*). A 95% ethanol extract of the fruits lowered elevated SGPT levels in mice treated with carbon tetrachloride or thioacetamide (*23*). Lignans, isolated from the fruits, have also been shown to have liver-protectant activities in vivo (*24, 25*). Intragastric administration of the lignans to mice, specifically 50.0 mg/kg bw of gomisin A, 50.0 mg/kg bw of gomisin B, 50.0–100.0 mg/kg bw of schisandrin A, 50–100.0 mg/kg bw of schisandrin B and 50.0–100.0 mg/kg bw of γ-schisandrin, decreased elevated SGPT levels in mice treated with carbon tetrachloride (*25*). Treatment with the lignans also prevented the elevation of SGPT levels and the morphological changes in the liver, such as inflammatory infiltration and liver cell necrosis, induced by carbon tetrachloride. Intragastric administration of 100 mg/kg bw of gomisin A, B or schisandrin also protected against thioacetamide-induced liver damage in mice (*23, 25*).

Oral pretreatment of rats with 50.0 mg/kg bw of gomisin A prevented the rise in SGPT and serum glutamic oxaloacetic transaminase (SGOT), as well as necrosis of hepatocytes induced by paracetamol (*26*). Intragastric administration of 30.0 mg/kg bw or 100.0 mg/kg bw of gomisin A per day for 4 days, increased liver weight in normal rats or animals with liver injury. Gomisin A suppressed the increase in serum transaminase activity and the appearance of histological changes, such as hepatocyte degeneration and necrosis, inflammatory cell infiltration and fatty depo-

sition induced by carbon tetrachloride, galactosamine or ethionine. Gomisin A also increased the activities of microsomal cytochrome B5, P450, NADPH cytochrome C reductase, aminophenazone-*N*-demethylase and 7-ethoxycoumarin *O*-deethylase, and decreased the activity of 3,4-benzopyrene hydroxylase (*27*).

Intragastric administration of 10.0–100.0 mg/kg bw of gomisin A per day for 4 days increased liver regeneration in rats after partial hepatectomy, increased the regeneration rate of the liver cells, and improved the serum retention rate of the foreign dye sulfobromophthalein. In addition, gomisin A enhanced the incorporation of radiolabelled phenylalanine into liver protein and decreased hexobarbital-induced sleeping time. Ultrastructural studies of liver tissue by electron microscopy showed an increase in rough and smooth endoplasmic reticulum in the groups receiving gomisin A. Gomisin A enhanced the proliferation of hepatocytes and the recovery of liver function after partial hepatectomy and increased hepatic blood flow. Liver enlargement induced by repeated administration of gomisin A may be due to the proliferation of endoplasmic reticulum (*27*). Intragastric administration of 10.0 mg/kg bw or 30.0 mg/kg bw of gomisin A per day for 3 or 6 weeks decreased fibrosis and accelerated liver regeneration and the recovery of liver function after partial hepatectomy in rats with chronic liver damage induced by carbon tetrachloride (*28*). Intragastric administration of 100.0 mg/kg bw of gomisin A per day for 14 days promoted hepatocyte growth after mitosis during regeneration of partially resected rat liver, and induced proliferation of non-parenchymal cells by increasing the c-*myc* product, a gene that precedes DNA replication in proliferating cells (*29*).

In vitro studies with cultured rat hepatocytes treated with an ethyl ether, ethyl acetate, methanol or water extract of the fruits, 0.1–1.0 mg/ml, reduced cytotoxicity induced by galactosamine and carbon tetrachloride (*30*). Gomisin A, 0.1 mg/ml, suppressed the biosynthesis of leukotrienes induced by calcium ionophore A2318 in rat peritoneal macrophages. This effect was partially associated with its antihepatotoxic effects (*31*).

Intragastric administration of 100.0–200.0 mg/kg bw of schisandrol A or schisandrin B reduced liver malondialdehyde formation induced by the administration of 50% ethanol to rats (*32*). Intragastric administration of 4.0–16.0 mg/kg bw of schisandrin B per day for 3 days increased the activities of hepatic glutathione *S*-transferase (GST) and glutathione reductase in mice treated with carbon tetrachloride (*33*). The mechanism by which schisandrin B exerts its hepatoprotectant effect appears to be through the enhancement of the hepatic glutathione antioxidant status in mice with carbon tetrachloride induced hepatotoxicity (*34, 35*). The ac-

tivities of glucose-6-phosphate dehydrogenase, selenium-glutathione peroxidase and γ-glutamylcysteine synthetase were reduced in a dose-dependent manner by schisandrin B (*33*). Pretreatment of mice with 1.0 mg/kg bw of schisandrin B per day for 3 days protected the animals against menadione-induced hepatic oxidative damage, and reduced the plasma level of alanine aminotransferase and the hepatic level of malondialdehyde as compared with menadione-intoxicated controls (*36*).

Intragastric administration of 12.0 mg/kg bw schisandrin B per day for 3 days to mice increased the hepatic mitochondrial glutathione concentration, whereas butylated hydroxytoluene decreased hepatic glutathione (*34*). Pretreatment with schisandrin B at the same dose sustained the hepatic mitochondrial glutathione level in carbon tetrachloride intoxicated mice and protected against carbon tetrachloride induced hepatotoxicity. Schisandrin B also increased the hepatic ascorbic acid (vitamin C) level in control animals, and sustained a high concentration of hepatic vitamins C and E in carbon tetrachloride intoxicated mice, which may partially explain its mechanism of action. Pretreatment of mice with intragastric administration of 1.2–12.0 mg/kg bw schisandrin B per day for 3 days had a dose-dependent protective effect on carbon tetrachloride induced lipid peroxidation and hepatocellular damage (*37*).

Administration of the powdered fruits in the diet, 5%, to mice induced a three-fold increase in activity of hepatic cytochrome P450. Total benzopyrene metabolism was increased 1.6-fold, and phenol II formation relative to total metabolites was significantly increased as compared with the control group. In addition, 7-ethoxycoumarin *O*-deethylase and aryl hydrocarbon hydroxylase activities were increased and the binding of aflatoxin to DNA was decreased (*38*).

Antioxidant activity

Inhibition of lipid peroxidation in rat liver microsomes was observed after treatment with schisandrol, schisandrin C and schisandrin B, 1.0 mmol/l, in vitro (*39*). Schisandrol and schisandrin B, 1.0 mmol/l, inhibited gossypol-induced superoxide anion generation in rat liver microsomes (*40*). Schisandrol, 1 mmol/l, scavenged oxygen radicals in human neutrophils induced by tetradecanoylphorbol acetate (*41*). Schisandrin B suppressed lipid peroxidation induced by carbon tetrachloride in hepatocytes in vitro (*42*). The release of GPT and lactate dehydrogenase was also reduced, thereby increasing hepatocyte viability and the integrity of the hepatocyte membrane (*39*). Schisandrin B, 10 mmol/l, inhibited NADPH oxidation in mouse liver microsomes incubated with carbon tetrachloride (*43*). Schisandrin B, 110.0 µmol/l, inhibited oxidation of erythrocyte membrane lipids induced by ferric chloride in vitro (*37*).

Antitumour activity

The effect of gomisin A on hepatocarcinogenesis induced by 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) in rats was assessed. Oral administration of 30 mg/kg bw of gomisin A per day for 5 weeks inhibited the appearance in the liver of foci for GST (placental form, GST-P), a marker enzyme of preneoplasm. Gomisin A also decreased the number of altered hepatic foci, such as the clear cell and basophilic cell type, in the early stages (*44, 45*). Administration of gomisin A in the diet, 0.03%, for 10 weeks decreased the concentration of GST-P, and the number and size of GST-P positive foci in the liver after treatment with 3'-MeDAB (*46*). This indicates that gomisin A may inhibit 3'-MeDAB-induced hepatocarcinogenesis by enhancing the excretion of the carcinogen from the liver and reversing the normal cytokinesis (*47*).

Central nervous system effects

Intraperitoneal administration of 10.0 mg/kg bw of a 50% ethanol extract of the fruits to mice potentiated the sedative effects of barbiturates (*48*). However, intraperitoneal administration of 5.0 mg/kg bw of an ethanol and petroleum ether extract of the fruits decreased barbiturate-induced sleeping times (*49*). Intraperitoneal administration of 50.0 mg/kg bw of an unspecified extract of the fruits to mice 30 minutes prior to the injection of pentobarbital, ethanol, or exposure to ether significantly reduced the sleeping time of the treated group by 41.4%, 51.5% and 27%, respectively ($P < 0.001$ for all differences) (*50*). However, other researchers have demonstrated that the effects of the fruits on pentobarbital sleeping time depended upon the time of administration, and the type of extract or individual schisandrin derivatives administered. Schisandrin B or schisandrol B, 12.5 mg/kg bw, administered 1 hour prior to the injection of pentobarbital potentiated sleeping time. However, if the compounds were administered 24 hours prior to injection of pentobarbital, a decrease in sleeping time was observed. Administration of schisandrin C prolonged pentobarbital-induced sleeping time regardless of when it was administered (*24*).

Effects on drug metabolism

The activity of the fruits in restoring hepatic drug metabolism and phase I oxidative metabolism in livers damaged by carbon tetrachloride was investigated in vivo by assessing the pharmacokinetics of antipyrine (*51*). Intragastric administration of 160.0 mg/kg bw of a lignan-rich extract of the fruits to rats 30 minutes prior to administration of carbon tetrachloride and a single dose of antipyrine improved antipyrine elimination, decreased its clearance and reduced the half-life of the drug. In addition,

normalization of the levels of SGPT and SGOT and cytochrome P450 was observed (*51*).

Intragastric administration of 200.0 mg/kg bw of schizandrin B and schisanhenol per day for 3 days increased liver GST and microsomal cytochrome P450 levels in mice and rats. Both compounds reduced an increase in uterus weight in animals treated with estradiol, and decreased serum estradiol levels in mice. An enhancement in metabolism by liver microsomes, specifically the induction of drug-metabolizing phase I and phase II enzymes was also noted (*52*).

Ergogenic effects

The effects of the fruits on fatigue in and the endurance of horses has been assessed in a number of small studies. In one study, a dried 50% ethanol extract of the fruits or saline solution (48 g) was administered orally to thoroughbred horses prior to an 800-m race at maximum speed and to polo horses before a 12-minute gallop at a speed of 400 m/min. Treatment of the animals with the extract reduced serum lactic acid levels and increased plasma glucose levels after the test. Horses treated with the extract were also able to run faster and completed the 800-m race in 50.4 seconds compared with 52.2 seconds for the control animals ($P < 0.05$), indicating an increase in physical performance (*53*).

In a randomized double-blind, crossover study, 12.0 g of a dried 50% ethanol extract of the fruits, standardized to contain 1.2% schizandrins, was administered orally to 20 race horses 30 minutes prior to competition. Horses treated with the extract had significantly reduced heart rates for up to 20 minutes following the race ($P < 0.01$). The rate of respiration was also reduced immediately after the race, and was maintained for 15 minutes ($P < 0.05$). In addition, plasma glucose concentrations increased significantly ($P < 0.05$) and concentrations of lactic acid were significantly lower ($P < 0.01$) in the treated group than in the control group. Treated horses also completed the circuit in a shorter time than controls (117.5 seconds compared with 120.3 seconds) (*54*). A placebo-controlled study involving 24 sports horses with performance problems, as well as high levels of serum γ-glutamyltransferase (SGT), SGOT and creatinine phosphokinase, assessed the effects of the fruits on performance. Oral administration of 3.0 g of a dried 50% ethanol extract of the fruits per day to 12 horses significantly reduced SGT, SGOT and creatinine phosphokinase levels ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively), and improved performance after 7 and 14 days, as compared with 12 placebo controls (*55*).

Intragastric administration of 1.6 g/kg bw of a petroleum ether extract of the fruits to rats significantly ($P < 0.01$) reduced exercise-induced elevation of plasma creatine phosphokinase (*56*).

Toxicology

Intragastric administration of 0.6 g/kg bw or 1.3 g/kg bw of the fruits per day for 10 days to mice resulted in only mild toxic effects, such as decreased physical activity, piloerection, apathy and an increase in body weight (*57*). The intragastric and intraperitoneal median lethal doses (LD_{50}) of a petroleum ether extract of the fruits in mice were 10.5 g/kg bw and 4.4 g/kg bw, respectively. The symptoms of toxicity included depressed motor activity, short cataleptic periods and a lack of coordination of motor functions, which were followed by tonic seizures and marked mydriasis (*58*). In a 7-day study, no deaths occurred after oral administration of high doses of schisandrins A and C (2000.0 mg/kg bw), and schisandrol A (500.0 mg/kg bw); schisandrol B (250.0 mg/kg bw) and schisandrin B (250.0 mg/kg bw) showed relatively higher levels of toxicity (*24*).

The toxicity of an ethanol extract containing schisandrin B, and of the schisandrins A and C, 2000.0 mg/kg bw) and schisandrol A, 1000.0 mg/kg bw, was reported after intragastric administration to mice. Death of mice occurred within 7 days after administration of schisandrins A and C. Schisandrol B, 500 mg/kg bw, is reported to have a relatively higher toxicity after intragastric administration to mice. The LD_{50} of schisandrol B in mice is reported to be 878.0 mg/kg bw by the intragastric route and 855.0 mg/kg bw after subcutaneous administration. The intragastric LD_{50} values for petrol-ether extracts with schisandrin contents of 10%, 40% and 80% were 10.5 g/kg bw, 2.8 g/kg bw and 1.4 g/kg bw, respectively (*4*).

Clinical pharmacology

Studies on healthy subjects

Oral administration of 5–10.0 mg/kg bw of a 70% ethanol extract of the fruits, reduced fatigue and increased the accuracy of telegraphic transmission and reception by 22% (*59*). In another study, healthy male volunteers were given an oral preparation of the fruit (dose and form not specified), and were required to thread a needle at the same time as taking a message delivered through headphones. The results demonstrated that when compared to other undefined stimulants, the extract increased the accuracy and quality of work (*57*).

Other uncontrolled investigations have demonstrated that oral administration of the fruits increases physical performance in human subjects. A decrease in fatigue and acceleration of recovery after exercise were reported for athletes, such as long-distance runners, skiers and gymnasts, after consuming 1.5–6.0 g of the fruits daily over a 2-week period (*60*).

The effect of the fruits on physical stress was investigated in a controlled study involving 59 airline stewardesses (aged 22–29 years) during seven nonstop 9-hour flights. The study measured several stress parameters before and after the flights, with and without treatment with 0.5 g of an undefined extract of the fruits. Control subjects displayed a significant increase in heart rate ($P < 0.001$) and blood pressure ($P < 0.01$) during flights, while those taking the extract did not. The report further described the effect of oral administration of 2.0 g of an extract of the fruits to 58 untrained soldiers (aged 19–23 years) and 62 highly trained sportsmen (aged 19–30 years). Physical work capacity as measured by a step-ergometer, significantly increased 24 hours after treatment ($P < 0.05$), while that of the controls remained the same (*61*).

A double-blind, placebo-controlled clinical trial assessed the effects of a standardized extract of the fruits on the concentration of nitric oxide in human saliva, blood neutrophils, lymphocytes and monocytes, and working capacity, as a measure of adaptogenic potential in heavy exercise. The level of nitric oxide in the saliva of beginner athletes was found to increase after exercise while that in the saliva of well-trained athletes was high and did not increase further after exercise. Tablets containing an extract of the fruits, 91.1 mg standardized to 3.1 mg of schisandrin and γ-schisandrin, were administered twice daily for 8 days. There was a significant increase in the pre-exercise levels of nitric oxide in both beginners ($n = 17$) and athletes ($n = 46$) ($P < 0.05$); there were no changes in the other parameters (*62*).

A placebo-controlled clinical trial involving 134 healthy subjects assessed the effects of a single administration of the encapsulated fruits on night vision and acceleration of adaptation to darkness. Visual function was assessed 15–20 minutes prior to administration and 3 hours after. Administration of a single dose of 3.0 g of the fruits increased visual acuity under low illumination and extended the visual field margins for white and red colours by 8–25° (*16*). In a second study of 150 subjects, a single administration of 3 g of the fruits increased visual acuity in 90% of subjects. Administration of the drug decreased the time recognition of an object in darkness (from 32.3 seconds to 18.4 seconds), 4.5 hours after administration (*63*).

Clinical trials in patients

In an uncontrolled study, a tincture of the fruits was used for the treatment of stomach and duodenal ulcers in 140 patients with acute and chronic ulcers, who had been ill for 1–10 years. Patients were treated with 30–40 drops per day for 3–4 weeks. All subjects reported a reduction in symptoms within a few days, with ulcer healing reported in 96.5% of patients after 35 days of treatment. Recurrent episodes of peptic ulcer

disease were reported in only 9 of 90 patients followed over a period of 1–6 years (*64*).

A review of the Chinese literature mentioned reports of more than 5000 cases of hepatitis treated with preparations of the fruits, which had resulted in reductions of elevated liver enzymes. Elevated SGPT activities returned to normal in 75% of treated patients after 20 days of treatment. In subjects with elevated SGPT due to drug toxicity, SGPT levels reportedly returned to normal in 83 of 86 cases after 1–4 weeks of treatment. Enzyme levels reportedly decreased even without the discontinuation of the hepatotoxic drugs (*17*). It must be stressed that these are uncontrolled observational studies with questionable methodology. Further well designed, controlled clinical trials are needed to ascertain their validity.

In a controlled trial involving 189 patients with chronic viral hepatitis B and elevated SGPT levels, an ethanol extract of the fruits, containing 20 mg of lignans and corresponding to 1.5 g of the fruits, was administered orally to 107 of the patients daily, while the control group (n = 82) received liver extracts and vitamins (*65*). Normal SGPT levels were observed in 72 (68%) of patients receiving the extract after 4 weeks. In the control group, normal SGPT levels were observed in 36 (44%), with an average recovery time of 8 weeks. However, improvements in SGPT were only temporary, and levels rose again 6–12 weeks after treatment was discontinued. Relapse rates were highest (46–69%) in chronic persistent hepatitis, elderly patients, and in those receiving long courses of treatment with hepatotoxic drugs. Most patients responded to resumption of treatment with a return to their previously reduced SGPT levels (*17, 65*).

Adverse reactions

Minor adverse effects such as heartburn, acid indigestion, stomach pain, anorexia, allergic skin reactions and urticaria have been reported (*66*).

Contraindications

No information available.

Warnings

Symptoms of overdose include restlessness, insomnia or dyspnoea (*67*).

Precautions

Drug interactions

The fruits may have depressant effects on the central nervous system and should not therefore be used in conjunction with other CNS depressants,

such as sedatives or alcohol. They have been shown to stimulate the activity of hepatic cytochrome P450 (*68*). While no drug interactions have been reported, co-administration of prescription drugs metabolized through cytochrome P450, such as cyclosporin, warfarin, protease inhibitors, St John's wort, estrogen and progesterone combinations, should only be undertaken under the supervision of a health-care provider, owing to the inductive effects of the fruits on phase I and II drug-metabolizing enzymes (*51, 52*).

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous or methanol extract of the fruits was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, or in the *Bacillus subtilis* H-17 recombination assay at concentrations of up to 100.0 mg/ml (*69, 70*).

Pregnancy: non-teratogenic effects

In one uncontrolled investigation, 20–25 drops of a tincture (70% ethanol) of the fruits were administered to pregnant women three times per day for 3 days. Induction of labour was observed after the second dose followed by an increase in active labour 2–3 hours after the initial induction. The activity was most pronounced in women who had previously given birth. Shortened labour times were reported and no negative effects regarding blood pressure, elimination of the placenta, or postnatal health of mother and infant were observed (*7, 71*). In another investigation, an increase in the amplitude of uterine contractions (28 mm compared with 5 mm in controls) and uterine tension was observed after subcutaneous administration of 0.1 ml/kg bw of a tincture of the fruits to pregnant rabbits. The activity was observed 1.5 hours after administration and persisted for 4 hours (*71*).

A study conducted on women living in the Bryansk region of Ukraine, near the site of the Chernobyl nuclear reactor accident, assessed the effects of adaptogen administration on the health status of developing fetuses in pregnant women exposed to constant low-level radiation. The symptoms of placental insufficiency improved, fetal protein status was stabilized, obstetric complications were reduced, and the health status of the newborn infants was improved. No substantiating data were provided in this report, and no information regarding the preparations or dosages administered or the effect of the preparation on uterine contractions was given (*7, 72*).

Owing to a lack of further safety data regarding the effect of Fructus Schisandrae on neonatal development, its use during pregnancy is not recommended (*7*).

Nursing mothers

Owing to a lack of safety data, the use of Fructus Schisandrae during nursing is not recommended.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic effects in pregnancy; or paediatric use.

Dosage forms

Dried fruits and tinctures, extracts and powders prepared from the fruits. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: 1.5–6.0 g of the dried fruits (*3*).

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Radix Scutellariae

Definition
Radix Scutellariae consists of the dried roots of *Scutellaria baicalensis* Georgi (Lamiaceae) (*1–4*).

Synonyms
Scutellaria grandiflora Adams, *S. lanceolaria* Miq., *S. macrantha* Fisch. (*5*). Lamiaceae are also known as Labiatae.

Selected vernacular names
Baical skullcap, huang chin, huang lien, huang qin, huangqin, hwanggum, hwang-keum, Koganebana, skullcap, senohgon, whang-geum, whangegum, wogon (*3, 6, 7*).

Geographical distribution
Indigenous to the Korean peninsula and to China, Japan, Mongolia and Russian Federation (*6, 8, 9*).

Description
A spreading perennial herb up to 20–60 cm high. Stems erect, tetragonal, branching near base, glabrous or pubescent in the stem margins. Leaves opposite, simple, with short petioles 2 mm long; limb lanceolate, 1.5–4.0 cm long, 5 mm wide; tip obtuse, entire. Flowers blue to purple, in racemes. Calyx campanulate, bilabiate, the superior lip with a crest at the back; corolla tube long, much longer than the calyx, enlarged towards the top, swelling at the base; limb bilabiate; stamens four, didymous, fertile, ascending under the superior lip; anthers ciliate; ovary superior. Fruits are collections of small tuberculate nutlets, nearly globular, leathery (*6, 8*).

Plant material of interest: dried roots
General appearance
Conical, twisted or flattened root, 5–25 cm long, 0.5–3.0 cm in diameter. Externally yellow brown, with coarse and marked longitudinal wrinkles,

and with scattered scars of lateral root and remains of brown periderm; scars of stem or remains of stem at the crown; xylem rotted in old roots; hard in texture and easily broken; fractured surface fibrous and yellow in colour, reddish-brown in the centre (*1–4*).

Organoleptic properties
Odour, slight; taste, slightly bitter (*1–4*).

Microscopic characteristics
To be established according to national requirements. For guideline to microscopic characteristics, see Powdered plant material.

Powdered plant material
Yellow brown. Fragments of parenchyma cells containing small amounts of starch grains, spheroidal, 2–10 µm in diameter, hila distinct. Elongated, thick-walled stone cells. Reticulated vessels numerous, 24–72 µm in diameter. Phloem fibres scattered singly or in bundles, fusiform, 60–250 µm long, 9–33 µm in diameter, thick-walled, with fine pit-canals. Cork cells brownish-yellow, polygonal. Fragmented wood fibres, about 12 µm in diameter, with oblique pits (*1–4*).

General identity tests
Macroscopic and microscopic examinations (*1–4*), microchemical tests (*1, 4*) and high-performance liquid chromatography for the presence of baicalin (*2, 4*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Total ash
Not more than 6% (*1–4*).

Acid-insoluble ash
Not more than 1% (*3*).

Water-soluble extractive
Not less than 40% (*3*).

Alcohol-soluble extractive
Not less than 15% (*3*).

Loss on drying
Not more than 12% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

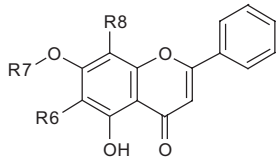
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

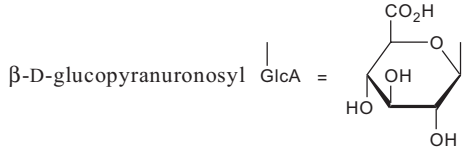
Other purity tests
Chemical, foreign organic matter and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 9.0% of baicalin determined by high-performance liquid chromatography (*4*). Other high-performance liquid chromatography methods are available (*2, 13*).

Major chemical constituents
The major constituents are flavonoids, chiefly baicalin (up to 14%) (*14*), baicalein (up to 5%) (*15*), wogonin (0.7%) (*15*) and wogonin-7-*O*-glucuronide (wogonoside, 4.0%) (*14, 16*). The structures of baicalin, baicalein and wogonin are presented below.



	R6	R7	R8
baicalein	OH	H	H
baicalin	OH	GlcA	H
wogonin	H	H	OCH_3



Medicinal uses

Uses supported by clinical data

None. Although clinical case reports suggest that Radix Scutellariae may stimulate the immune system and induce haematopoiesis (*17–19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Treatment of fever, nausea and vomiting, acute dysentery, jaundice, coughs, carbuncles and sores, and threatened abortion (*3, 4*).

Uses described in traditional medicine

Treatment of allergies, arteriosclerosis, diarrhoea, dermatitis and hypertension (*7*).

Pharmacology

Experimental pharmacology

Antihepatotoxic activity

Intragastric administration of 400.0 mg/kg body weight (bw) of an aqueous extract of Radix Scutellariae to rats prevented increases in the activities of liver enzymes, such as alkaline phosphatase, lactate dehydrogenase and alanine aminotransferase, induced by carbon tetrachloride or galactosamine (*20*). Baicalein, 185.0 µmol/l, inhibited the proliferation of cultured hepatic stellate cells (*21*). Baicalein, 10.0 µmol/l, also significantly ($P < 0.001$) decreased the incorporation of tritiated thymidine in cultured rat hepatic stellate cells stimulated with platelet-derived growth factor-B subunit homodimer or fetal calf serum (*22*).

Anti-inflammatory activity

External application of 0.5 mg/ear of a 50% ethanol extract of the roots to the ears of mice with ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate or arachidonic acid significantly reduced inflammation ($P < 0.01$) (*23*). The anti-inflammatory effect of baicalein in treating chronic inflammation in rats with adjuvant-induced arthritis (median effective dose (ED_{50}) 120.6 mg/kg bw, intragastric route) was superior to that in carrageenan-induced footpad oedema (ED_{50} 200.0 mg/kg bw, intragastric route) (*24*). Baicalein also inhibited leukotriene C4 biosynthesis in vitro in rat resident peritoneal macrophages stimulated with calcium ionophore A23187, median inhibitory concentration (IC_{50}) 9.5 µm (*24*). Three flavonoids isolated from the roots, wogonin, baicalein and baicalin, 1.0 µg/ml, inhibited lipopolysaccharide-induced production of interleukin-1β in human gingival fibroblasts by 50% (*25*). The effects of nine

flavonoids, isolated from the roots, on adhesion molecule expression induced by interleukin-1β and tumour necrosis factor-α in cultured human umbilical vein endothelial cells were assessed. Baicalein only showed a dose-dependent inhibition of the induced expression of endothelial leukocyte adhesion molecule-1 and intracellular adhesion molecule-1, with 50% inhibition observed at concentrations of 0.23 µmol/l and 0.4 µmol/l, respectively. These data suggest that Radix Scutellariae may exert its anti-inflammatory effects through the inhibition of leukocyte adhesion to the endothelium (*26*). Baicalin has been shown to inhibit the binding of chemokines to human leukocytes and cells transfected with chemokine receptors. Coinjection of baicalin with CXC chemokine interleukin-8 into rat skin inhibited neutrophil infiltration elicited by interleukin-8 (*27*).

Antioxidant activity

The free-radical scavenging and antioxidant activities of baicalein, baicalin, wogonin and wogonoside were tested in vitro. Electron spin resonance results showed that baicalein and baicalin scavenged hydroxyl radical and alkyl radical in a dose-dependent manner, while wogonin and wogonoside had no effect. Baicalein and baicalin, 10 µmol/l, inhibited lipid peroxidation of rat brain cortex mitochondria induced by Fe(2+)/ascorbic acid or NADPH, while wogonin and wogonoside had effects only on NADPH-induced lipid peroxidation. In a study on cultured human neuroblastoma SH-SY5Y, baicalein and baicalin, 10 µmol/l, protected cells against hydrogen peroxide-induced injury (*28*). An aqueous extract of the roots or baicalein, 25–100 µmol/l, significantly ($P < 0.001$) attenuated ischaemia/reperfusion oxidative stress in cultured chick embryonic ventricular cardiomyocytes. Cell death due to ischaemia/reperfusion injury decreased from 47% to 26% in treated cells. After treatment of the cells with antimycin A, an extract of the roots decreased cell death to 23% in treated cells compared with 47% in untreated cells (*29*).

Pretreatment with ganhuangenin, isolated from the roots, suppressed the formation of phosphatidylcholine hydroperoxide initiated by the peroxyl-generating oxidant, 2,2'-azobis-2-aminopropane hydrochloride (*30*). Baicalein, 5.0–25.0 µmol/l, and wogonin, 5.0–50.0 µmol/l, inhibited lipopolysaccharide-induced nitric oxide generation in a macrophage-derived cell line, RAW 264.7 in a concentration-dependent manner. The same two compounds, 25.0 µmol/l, also inhibited protein expression of inducible nitric oxide synthase (*31*).

Antimicrobial activity

An aqueous or methanol extract of the roots, 200 µg/ml, elicited significant inhibition (> 90%) ($P < 0.01$) of the activity of human immuno-

deficiency virus type-1 protease (*32*). Baicalein inhibited the growth of *Fusarium oxysporum* and *Candida albicans* in vitro, minimum inhibitory concentrations 0.112 g/l and 0.264 g/l, respectively (*33*).

A hot aqueous extract of the roots inhibited the growth of *Alcaligenes calcoaceticus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus* at concentrations of 200.0–400.0 µg/ml but was not active against *Escherichia coli* in vitro at concentrations of up to 1600.0 µg/ml (*34*).

A hot aqueous extract of the roots, 0.25–1.0 µg/ml, inhibited the growth of *Actinomyces naeslundii*, *A. odontolyticus, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Bacteroides gingivalis, B. melaninogenicus* and *Streptococcus sanguis* (*35*).

Antitumour activity

The in vitro effects of baicalin on growth, viability, and induction of apoptosis in several human prostate cancer cell lines, including DU145, PC3, LNCaP and CA-HPV-10 were investigated. Baicalin inhibited the proliferation of prostate cancer cells but the responses were different in the different cell lines. DU145 cells were the most sensitive and LNCaP cells the most resistant. Baicalin caused a 50% inhibition of DU145 cells at concentrations of 150 µg/ml or higher. Inhibition of prostate cancer cell proliferation by baicalin was associated with induction of apoptosis (*36*). Baicalein inhibited the proliferation of estrogen receptor-positive human breast cancer MCF-7 cells in vitro, median effective concentration 5.3 µg/ml (*37*).

Antiviral activity

Baicalin inhibited retroviral reverse transcriptase activity in human immunodeficiency virus type 1 (HIV-1) activity in infected H9 cells, as well as HIV-1 specific core antigen p24 expression and quantitative focal syncytium formation on CEM-SS monolayer cells. Baicalin was a noncompetitive inhibitor of HIV-1 reverse transcriptase, IC_{50} 22.0 µmol/l. It also inhibited reverse transcriptase from Maloney murine leukaemia virus, Rous-associated virus type 2 and cells infected with human T-cell leukaemia virus type I (HTLV-I) (*38*). A flavone, 5,7,4'-trihydroxy-8-methoxyflavone, isolated from the roots, inhibited the activity of influenza virus sialidase but not mouse liver sialidase in vitro (*39*). The compound also had anti-influenza virus activity in Madin-Darby canine kidney cells, in the allantoic sac of embryonated eggs (IC_{50} 55.0 µmol/l) and in vivo in mice (*39–41*). The compound, 50.0 µmol/l, was also shown to reduce the single-cycle replication of mouse-adapted influenza virus A/PR/8/34 in Madin-Darby canine kidney cells by inhibiting the fusion of the virus

with endosome/lysosome membrane and the budding of the progeny virus from the cell surface in the virus infection cycle (*42*). Baicalein produced a concentration-dependent inhibition of HTLV-I replication in infected T and B cells, as well as inhibiting the activity of reverse transcriptase in cells infected with HTLV-I (*43*). The mechanism by which baicalin exerts its anti-HIV-1 activities appears to involve the binding of baicalin to form complexes with selected cytokines and attenuates their ability to bind and activate receptors on the cell surface. Baicalin also binds to the HIV-1 envelope proteins and the cellular CD4 and chemokine co-receptors, thereby blocking HIV-1 entry into the cell (*44*).

Central nervous system activity

Four chemical constituents isolated from the roots bound to the benzodiazepine-binding site of the γ-aminobutyric acid A receptor as follows; wogonin (2.03 µmol/l) > baicalein (5.69 µmol/l) > scutellarein (12.00 µmol/l) > baicalin (77.00 µmol/l) (*45*). Results of a benzodiazepine-binding assay showed that three flavones, baicalein, oroxylin A and skullcapflavone II, from an aqueous extract of the roots bound to the benzodiazepine-binding site with Ki values of 13.1 µmol/l, 14.6 µmol/l and 0.36 µmol/l, respectively (*46*).

Intragastric administration of an aqueous extract of the roots (dose not specified) to rats produced an increase in cutaneous vasodilation resulting in a fall in rectal temperature. No changes in metabolic rate or respiratory evaporative heat loss were observed (*47*).

Enzyme inhibition

Baicalin inhibited the activity of aldose reductase isolated from bovine testes, inhibitory concentration 5.0 µg/ml (*48*).

Immunological effects

Treatment of mouse peritoneal macrophages with an aqueous extract of the roots, 0.1–100.0 µg/ml, following treatment with recombinant interferon-γ, resulted in a significant ($P < 0.05$) increase in the production of nitric oxide (*49*). However, a decoction of the roots inhibited nitric oxide production induced by lipopolysaccharide treatments of murine macrophages, IC_{50} 20.0 µg/ml (*50*).

Platelet aggregation inhibition

A 1-butanol, chloroform or ethyl acetate extract of the roots, 400.0 µg/ml, inhibited platelet-activating factor binding to rabbit platelets in vitro (*51*). An aqueous or hexane extract of the roots, 5.0 mg/ml, inhibited platelet aggregation induced by arachidonic acid, adenosine diphosphate and collagen in rat platelets in vitro (*52, 53*). Baicalein dose-dependently

inhibited production of plasminogen activator inhibitor-1 in cultured human umbilical vein endothelial cells induced by treatment with thrombin and thrombin receptor agonist peptide, IC_{50} values 6.8 µmol/l and 3.5 µmol/l, respectively (*54*).

Smooth muscle effects

The vascular effect of purified baicalein was assessed in isolated rat mesenteric arteries. Baicalein exerted both contractile and relaxant effects on the thromboxane receptor agonist U46619-, phenylephrine- or high potassium-contracted endothelium-intact arteries. In endothelium-denuded arteries, the contractile response to baicalein, 0.3–10 µmol/l, was absent while the relaxant response to baicalein, 30–300.0 µmol/l, remained. Pretreatment with 100.0 µmol/l of NG-nitro-L-arginine (L-NNA) abolished the effect. Pretreatment with baicalein, 3–10.0 µmol/l, attenuated relaxation induced by acetylcholine or calcium ionophore A23187. At low concentrations, baicalein caused a contractile response and inhibited the endothelium-dependent relaxation, probably through inhibition of endothelial nitric oxide formation/release. At higher concentrations, baicalein relaxed the arterial smooth muscle, partially through inhibition of protein kinase C (*55*).

Toxicology

Intragastric administration of 10.0 g/kg bw of a decoction of the roots or intravenous administration of 2.0 g/kg bw of an ethanol extract to rabbits induced sedation but no toxic effects were observed (*17*). Intravenous administration of 2.0 g/kg bw of an aqueous extract of the roots to rabbits initially produced sedation. However, 8–12 hours later all the animals died. When the dose was decreased to 1.0 g/kg bw no deaths occurred. The median oral lethal dose (LD_{50}) of a 70% methanol extract of the roots in mice was > 2.0 g/kg (*56*).

Intragastric administration of 12.0–15.0 g/kg bw of an aqueous extract of the roots to dogs caused emesis but no other toxic effects. Oral administration of 4.0–5.0 g/kg bw of the same extract three times per day for 8 weeks to dogs did not cause any toxic effects. The subcutaneous LD_{50} in mice was 6.0 g/kg bw for an ethanol extract of the roots, 6.0 g/kg bw for baicalin and 4.0 g/kg bw for wogonin (*17*). The intraperitoneal LD_{50} of baicalin in mice was 3.1 g/kg bw (*17*).

Clinical pharmacology

Chemotherapy of patients with lung cancer is associated with a decrease in immune function owing to a decrease in the relative number of T-lymphocytes. Administration of a dry extract of the roots to cancer patients

receiving chemotherapy produced a tendency towards an increase in lymphocytes. The immunoregulation index in this case was approximately twice the background values during the whole period of investigation. The inclusion of the roots in the therapeutic regimen promoted an increase in the level of immunoglobulin A and stabilized the concentration of immunoglobulin G (no further details available) (*19*).

A decoction of the roots was used to treat upper respiratory infections in children up to 5 years old and younger. The dose administered was 6.0 ml for children under the age of 1 year, and 8.0–10.0 ml for children up to 5 years of age. Of 63 cases (51 with respiratory tract infections, 11 with acute bronchitis, and one with acute tonsillitis), 51 showed benefit, and body temperature normalized after 3 days of treatment (*17*).

Haematopoiesis was studied in 88 patients with lung cancer during antitumour chemotherapy given in combination with a dry extract of the roots. Oral administration of the roots induced haematopoiesis, intensification of bone-marrow erythro- and granulocytopoiesis and an increase in the content of circulating precursors of erythroid and granulomonocytic colony-forming units (*18*).

Adverse reactions

Rare gastrointestinal discomfort and diarrhoea are associated with oral administration of Radix Scutellariae (*17*). Although liver damage due to administration of the roots has been suggested (*57*), no direct correlations of ingestion of the roots to any published cases of liver damage have been published.

Contraindications

Owing to possible teratogenic and mutagenic effects (*58, 59*), and a lack of safety data, use of Radix Scutellariae is contraindicated during pregnancy and nursing and in children under the age of 12 years.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of Radix Scutellariae, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 (*59, 60*). However, intraperitoneal administration of 4.0 mg/

kg bw of the aqueous extract to mice, equal to 10–40 times the amount used in humans, was mutagenic (*59*).

Pregnancy: teratogenic effects
Intragastric administration of 500.0 mg/kg bw of a 70% methanol extract of the roots daily to rats starting on the 13th day of pregnancy had no teratogenic or abortifacient effects (*56*). An aqueous extract of the roots, 24.98 g/kg bw, given by intragastric administration to pregnant rats on days 8–18 of pregnancy was teratogenic (*58*).

Pregnancy: non-teratogenic effects
Intragastric administration of 24.98 g/kg bw of an aqueous extract of the roots to pregnant rabbits on days 8–18 of pregnancy had no abortifacient effects (*58*). A methanol extract of the roots, 1.0 mg/ml, inhibited oxytocin-induced contractions in isolated rat uterus (*61*).

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Dried roots, extracts, infusions and decoctions. Store in a well closed container in a cool, dry place, protected from moisture (*4*).

Posology
(Unless otherwise indicated)
Daily dose: 3–9 g of dried roots as an infusion or decoction (*4*).

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Radix cum Herba Taraxaci

Definition

Radix cum Herba Taraxaci consists of the entire plant of *Taraxacum officinale* Weber ex Wiggers (Asteraceae) (*1–3*).[1]

Synonyms

For *Taraxacum officinale*: *Leontodon officinale* With., *L. taraxacum L. Taraxacum officinale* (With.) Wigg., *T. dens leonis* Desf., *T. vulgare* Schrank, (*6*).

Selected vernacular names

Ackerzichorie, amargon, blowball, Butterblume, cankerwort, capo di frate, chicoria amarga, cicoria sarvatica, cicouureya de la bonne, cicoureya deis prats, dandelion, dent-de-lion, dente di leone, dhudal, diente de leon, dhorsat al ajouz, dudhi, engraissa-porc, florion d'or, gol ghased, Gemeiner Löwenzahn, gobesag, Irish daisy, hindabaa beri, hokgei, kanphul, kanphuli, kasni sahraii, Kettenblume, khass berri, Kuhblume, lagagna, laiteron, lechuguilla, lion's tooth, Löwenzahn, maaritpauncin, marrara, milk gowan, min-deul-rre, monk's head, mourayr, mourre de por, mourre de pouerc, oduwantschiki, paardebloem, patalagagna, peirin, Pfaffendistel, Pfaffenröhrlein, Pferdeblume, pilli-pilli, piochoublit, piss-a-bed, pissa-chin, pissanliech, pissenlit, poirin, po-kong-young, porcin, pu gong ying, puffball, pugongying, Pusteblume, ringeblume, salatta merra, sanalotodo, saris berri, seiyo-tanpopo, sofione, srissi, tarakh-chaqoune, tarkhshaquin, tarassaco, taraxaco, telma retaga, Wiesenlattich, witch gowan, yellow gowan (*4–10*).

Geographical distribution

Taraxacum officinale is indigenous to the northern hemisphere (*11*). *T. mongolicum, T. sinicum* and related species are found in the Korean peninsula and China (*4, 5*).

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[1] *Taraxacum mongolicum* Hand.-Mazz. and *T. sinicum* Kitag. are also recognized in the *Pharmacopoeia of the People's Republic of China* (*4*) and the *Pharmacopoeia of the Republic of Korea* (*5*).

Description

A perennial herb consisting of an underground, long, straight, tapering, fleshy brown root, which is continued upward as a simple or branched rhizome. From the rhizome arises a rosette of bright-green runcinate leaves and later, from the centre of the rosette, a hollow scape, 6–30 cm high bearing on its summit a broad orange-yellow head of ligulate flowers. Fruits are fusiform, greenish-brown achenes, terminating in a slender stalk crowned by a silky, spreading pappus, and borne on a globular fruiting head (*12*).

Plant material of interest: dried whole plants

General appearance

A crumpled and rolled mass. Roots conical, frequently curved, tapering, often broken into irregular pieces, externally brown. Root stock with brown or yellowish-white hairs. Leaves basal, frequently crumpled and broken; when whole, oblanceolate, greenish-brown or dark green with a pronounced midrib; apex acute or obtuse; margins lobate or pinnatifid. Pedicels one or more, each with a capitulum; involucre several rows, the inner row relatively long; corolla yellowish-brown or pale yellowish-white (*1, 4, 5*).

Organoleptic properties

Odour, slight; taste, slightly bitter (*1, 11*).

Microscopic characteristics

Epidermal cells on both leaf surfaces have sinuous anticlinal walls, cuticle striations distinct or sparsely visible. Both leaf surfaces bear non-glandular hairs with three to nine cells, 17–34 µm in diameter. Stomata, occurring more frequently on the lower surface, anomocytic or anisocytic, with three to six subsidiary cells. Mesophyll contains fine crystals of calcium oxalate. Transverse section of root shows cork with several layers of brown cells. Phloem broad, groups of laticiferous tubes arranged in several interrupted rings. Xylem relatively small, with indistinct rays, vessels large, scattered. Parenchymatous cells contain inulin (*1*).

Powdered plant material

Greenish yellow. Large root parenchymatous cells, brown reticulate vessels and tracheids and non-lignified fibres. Leaf fragments with sinuous, anticlinal-walled epidermal cells and a few anomocytic stomata. Numerous narrow annular thickened vessels and fragments of brown laticiferous tissues (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*, *4*, *5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 17% (*3*).

Water-soluble extractive

Not less than 30% (*3*).

Loss on drying

Not more than 11% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

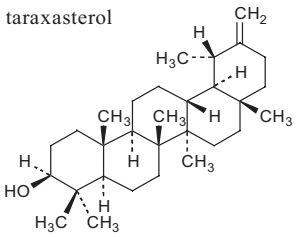
Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

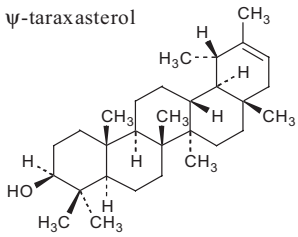
Chemical assays

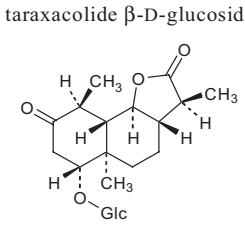
To be established in accordance with national requirements.

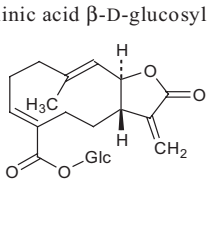
Major chemical constituents

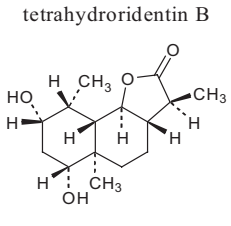
The characteristic constituents are sesquiterpenes, including the bitter eudesmanolides tetrahydroridentin B and taraxacolide β-D-glucopyranoside; and the germacranolides, taraxinic acid β-D-glucopyranoside and 11,13-dihydrotaraxic acid β-D-glucopyranoside. Also present are the *p*-hydroxyphenylacetic acid derivative, taraxacoside; the triterpenes, taraxasterol, ψ-taraxasterol and taraxerol; and inulin (2–40%) (*4, 10, 11*). Representative structures are presented below.

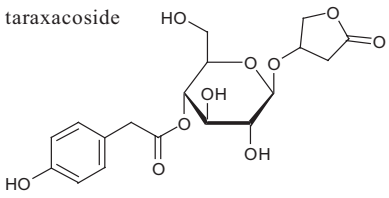


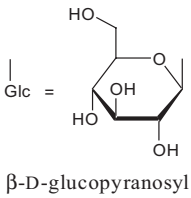












Medicinal uses

Uses supported by clinical data

No information available.

Uses described in pharmacopoeias and well established documents

To stimulate diuresis (*2, 5*), increase bile flow and stimulate appetite, and for treatment of dyspepsia (*2*).

Uses described in traditional medicine

As a galactagogue, laxative and tonic. Treatment of boils and sores, diabetes, fever, inflammation of the eye, insomnia, sore throat, lung abscess, jaundice, rheumatism and urinary tract infections (*10*).

Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity

External applications of 2.0 mg/ear of a methanol extract of the dried leaves to mice reduced ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (*16*). Intragastric administration of 1.0 g/kg body weight (bw) of a 95% ethanol extract of the whole plant to mice inhibited benzoquinone-induced writhing (*17*). Intraperitoneal administration of 100.0 mg/kg bw of a 95% ethanol extract of the whole plant to mice inhibited carrageenan-induced footpad oedema by 42%, and reduced pain as measured by the hot-plate test and benzoquinone-induced writhing (*17*). Intragastric administration of 100.0 mg/kg bw of an 80% ethanol extract of the dried roots to rats inhibited carrageenan-induced footpad oedema by 25%, compared with 45% inhibition resulting from administration of 5.0 mg/kg bw of indometacin (*18*).

Antimicrobial activity

A 95% ethanol extract of the dried aerial parts, 1.0 mg/ml, did not inhibit the growth of *Bacillus globifer*, *B. mycoides, B. subtilis, Escherichia coli, Fusarium solani, Klebsiella pneumoniae, Penicillium notatum, Proteus morganii, Pseudomonas aeruginosa, Salmonella gallinarum, Serratia marcescens, Staphylococcus aureus, Mycobacterium smegmatis* or *Candida albicans* in vitro (*19, 20*). No antibacterial effects were observed using a 50% ethanol extract of the whole plant, 50 µl/plate, against *Escherichia coli, Salmonella enteritidis, Salmonella typhosa, Shigella dysenteriae* or *Shigella flexneri* (*21*).

Antiulcer activity

Intragastric administration of 2.0 g/kg bw of an aqueous extract of the whole plant to rats protected the animals against ethanol-induced gastric ulceration. A methanol extract, however, was not active (*22*).

Choleretic activity

Intragastric administration of an aqueous or 95% ethanol extract of the whole plant (dose not specified) to rats increased bile secretion by 40% (*23*).

Diuretic activity

Intragastric administration of 8.0–50.0 ml/kg bw of a 95% ethanol extract of the whole plant to rats induced diuresis and reduced body weight (*24*). Intragastric administration of 0.1 ml/kg bw of a 30% ethanol extract of the whole plant to mice induced diuresis (*25*). However, intragastric

administration of 50.0 mg/kg bw of a chloroform, methanol or petroleum ether extract of the roots to mice did not consistently increase urine output (*26*).

Hypoglycaemic activity

Intragastric administration of a 50% ethanol extract of the whole plant to rats, 250.0 mg/kg bw, or rabbits, 1.0 g/kg bw, reduced blood glucose concentrations (*27*). However, intragastric administration of 2.0 g/kg bw of the powdered whole plant to rabbits did not reduce blood sugar concentrations in alloxan-induced hyperglycaemia (*28*). Intragastric administration of 25.0 mg/kg bw of an aqueous extract of the dried root to mice reduced glucose-induced hyperglycaemia (*29, 30*). However, a decoction or 80% ethanol extract of the dried roots had no effect (*30*).

Immunological effects

Intragastric administration of 3.3 g/kg bw of an aqueous extract of the whole plant to mice daily for 20 days significantly ($P < 0.01$) decreased cyclophosphamide-induced immune damage (*31*). Treatment of scalded mice with suppressed immune functions with an aqueous extract of the whole plant (dose and route not specified) stimulated the immune response (*32*). Nitric oxide synthesis inhibition induced by cadmium in mouse peritoneal macrophages stimulated with recombinant interferon-γ and lipopolysaccharide was counteracted by treatment of the cells with an aqueous extract of the whole plant, 100 µg/ml. The results were mainly dependent on the induction of tumour necrosis factor-α (TNF-α) secretion stimulated by the aqueous extract (*33*). Treatment of primary cultures of rat astrocytes with an aqueous extract of the whole plant, 100.0 µg/ml, inhibited TNF-α production induced by lipopolysaccharide and substance P. The treatment also decreased the production of interleukin-1 in astrocytes stimulated with lipopolysaccharide and substance P. The study indicated that Radix cum Herba Taraxaci may inhibit TNF-α production by inhibiting interleukin-1 production, thereby producing anti-inflammatory effects (*34*). Treatment of mouse peritoneal macrophages with an aqueous extract of the whole plant, 100 µg/ml, after treatment of the cells with recombinant interferon-γ, resulted in increased nitric oxide synthesis owing to an increase in the concentration of inducible nitric oxide synthase. The results were dependent on the induction of TNF-α secretion by Radix cum Herba Taraxaci (*35*).

Toxicology

The intraperitoneal median lethal dose (LD_{50}) of a 95% ethanol extract of the whole plant in rats was 28.8 mg/kg bw (*24*). In rats, the maximum

tolerated dose of a 50% ethanol extract of the whole plant administered by the intraperitoneal route was 500.0 mg/kg bw (*27*). No visible signs of toxicity were observed in rabbits after intragastric administration of the powdered whole plant at doses of 3–6 g/kg bw per day for up to 7 days (*36*).

Clinical pharmacology
No information available.

Adverse reactions
Allergic reactions including anaphylaxis and pseudoallergic contact dermatitis have been reported (*37–40*). Cross-reactivity has been reported in individuals with an allergy to the pollen of other members of the Asteraceae (*41*).

Contraindications
Radix cum Herba Taraxaci is contraindicated in obstruction of the biliary or intestinal tract, and acute gallbladder inflammation. In case of gallbladder disease, Radix cum Herba Taraxacum should only be used under the supervision of a health-care professional (*2*).

Warnings
May cause stomach hyperacidity, as with all drugs containing amaroids (*2*).

Precautions
Drug interactions
A decrease in the maximum plasma concentration of ciprofloxacin was observed in rats treated with concomitant oral administration of 2.0 g/kg bw of an aqueous extract of the whole plant and 20.0 mg/kg bw of ciprofloxacin (*42*).

Carcinogenesis, mutagenesis, impairment of fertility
No effects on fertility were observed in female rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Pregnancy: teratogenic effects
No teratogenic or embryotoxic effects were observed in the offspring of rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried whole plant, native dry extract, fluidextract and tincture (*1, 2*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: 3–4 g of cut or powdered whole plant three times; decoction, boil 3–4 g of whole plant in 150 ml of water; infusion, steep 1 tablespoonful of whole plant in 150 ml of water; 0.75–1.0 g of native dry extract 4:1 (w/w); 3–4 ml fluidextract 1:1 (g/ml) (*2*); 5–10 ml of tincture (1:5 in 45% alcohol) three times (*1*).

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Semen Trigonellae Foenugraeci

Definition

Semen Trigonellae Foenugraeci consists of the dried ripe seeds of *Trigonella foenum-graecum* L. (Fabaceae) (*1–7*).

Synonyms

Buceras foenum-graecum (L.) All., *Foenum-graecum officinale* Moench, *F. officinale* Moench var. *cultum* Alef., *F. sativum* Med., *Folliculigera graveolens* Pasq., *Tels foenum-graecum* (L.) Kuntze, *Trigonella foenum-graecum* L. subsp. *culta* (Alef.) Gams, *T. graeca* St Lag. and *T. jemenensis* (Serp.) Sinsk. (*8*). Fabaceae are also known as Leguminosae.

Selected vernacular names

Alholvabockshorn, bahubeeja, bahupatrika, bhaji, Bockshornklee, bothinee, boukeros, bukkehorn, chamliz, chanbalid, chanbalila, chanbalit, chandrika, chilebe, deepanee, el halbah, fariqua, feenugreek, fenacho, fenigrek, fenogreco, fenogreco, fénugrec, fenugreek, fenugriego, fieno-greco, foenugreek, fumugrec, gandhaphala, goat's horn, Greek hay, halba, halbet, hay trigonella, helba, henogriego, hilba, hinojogriego, hoolbah, hula-pa, hulba, huluba, hulupa, jyoti, kelabat, kelabet, klabet, koroha, kozieradka pospolita, Kuhhornklee, kunchika, l-helba, maithi, maithy, mathi, menle, mentepale, menthiam, menthi, menti-kuroa, methi, methika, methiky, methini, methra, methuka, methisak, mentikoora, mentulu, methun, methy, mitha, monte soffu, munichhada, pe-nam-ta-zi, penan-ta, peetabeeja, samli, schöne Margret, schöne Marie, senegré, shamlit, shamlid, shamlitz, shanbalileh, shandalid, thenthya, tifidas, tilis, uluhaal, uluva, vendayam, venthiam, ventayam (*1, 4, 8–12*).

Geographical distribution

Indigenous to the Mediterranean region, China, India and Indonesia. Cultivated in these countries (*5, 13*).

Description

Annual aromatic herb, up to 60 cm high with a well developed taproot and much branched roots. Stem solitary or basally branched, terete, slightly pubescent, green to purple. Leaves petiolate, alternate, trifoliolate; stipules triangular, small, adnate to the petiole. Rachis short. Leaflets obovate or oblong, 1.5–4.0 cm long, 0.5–2.0 cm wide, upper part of margin denticulate. Flowers whitish, solitary, axillary, subsessile, 12–15 mm long. Calyx campanulate, finely pubescent, tube 4.5 mm long, with five lobes. Pistil with sessile ovary, glabrous style and capitate stigma. Fruits straight to occasionally sickle-shaped, linear pods, glabrous, with fine longitudinal veins, terminating in a beak 2–3 cm long. Seeds oblong-rhomboidal, 3–5 mm long and 2–3 mm wide, with a deep furrow dividing each into two unequal lobes, with rounded corners, rather smooth, brownish (*11*).

Plant material of interest: dried ripe seeds

General appearance

Oblong-rhomboidal, 3.0–5.0 mm long, 2.0–3.0 mm wide, 1.5–2.0 mm thick, with rounded corners, rather smooth. Yellowish-brown to reddish-brown, with a deep furrow dividing each seed into two unequal lobes, and a deep hilum at the intersection of the two furrows. Texture hard, not easily broken. Testa thin, endosperm translucent and viscous; cotyledons two, pale yellow, radicle curved, plump and long (*1, 6, 7, 11*).

Organoleptic properties

Odour: characteristic, aromatic; taste: slightly bitter (*1, 2, 6, 7*).

Microscopic characteristics

Transverse section shows an epidermis of palisade cells, one layer, with thick cuticle and thick lamellated walls, and a relatively large lumen at the lower part. Longitudinal pit-canals fine and close. Subepidermal layer of basket-like cells, with bar-like thickening on the radial walls, followed by a parenchymatous layer. Endosperm of several layers of polyhedral cells with stratified mucilaginous contents and thickened walls. Cotyledons of parenchymatous cells containing fixed oil and aleurone grains up to 15 µm in diameter (*1, 2, 7*).

Powdered plant material

Yellowish-brown showing fragments of the testa in sectional view with thick cuticle covering epidermal cells, with an underlying hypodermis of large cells, narrower at the upper end and constricted in the middle, with bar-like thickenings of the radial walls. Yellowish-brown fragments of the epidermis

in surface view, composed of small polygonal cells with thickened and pitted walls, frequently associated with the hypodermal cells, circular in outline with thickened walls. Fragments of the hypodermis viewed from below, composed of polygonal cells with bar-like thickenings extending to the upper and lower walls. Parenchyma of the testa with elongated, rectangular cells with slightly thickened walls. Fragments of endosperm with irregularly thickened, sometimes elongated cells, containing mucilage (*1, 2, 6*).

General identity tests

Macroscopic and microscopic examinations (*1, 2, 5–7, 11*), microchemical tests (*5*), and thin-layer chromatography for the presence of trigonelline (*5, 6*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 2% (*1, 2, 4, 6*).

Total ash

Not more than 5% (*3, 6*).

Acid-insoluble ash

Not more than 2% (*1, 2, 5*).

Water-soluble extractive

Not less than 35% (*5*).

Alcohol-soluble extractive

Not less than 5% (*4*).

Loss on drying

Not more than 12% (*6*).

Swelling index

Not less than 6 (*3, 6*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia*

(*15*) and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

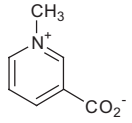
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

To be established in accordance with national requirements.

Major chemical constituents

Semen Trigonellae Foenugraeci is rich in mucilage (25–45%) and contains a small amount of essential oil (0.01%) and a variety of secondary metabolites, including protoalkaloids, trigonelline (up to 0.37%), choline (0.05%); saponins (0.6–1.7%) derived from diosgenin, yamogenin, tigogenin and other compounds; sterols including β-sitosterol; and flavonoids, among which are orientin, isoorientin and isovitexin (*8, 12, 13, 17*). The structure of trigonelline is presented below.

trigonelline 

Medicinal uses

Uses supported by clinical data

As an adjunct for the management of hypercholesterolaemia, and hyperglycaemia in cases of diabetes mellitus (*18–21*). Prevention and treatment of mountain sickness (*22*).

Uses described in pharmacopoeias and well established documents

Internally for loss of appetite, and externally as a poultice for local inflammations (*23*). Treatment of pain, and weakness and oedema of the legs (*7*).

Uses described in traditional medicine

As an aphrodisiac, carminative, diuretic, emmenagogue, emollient, galactagogue and tonic (*12, 23*). Treatment of abdominal colic, bronchitis, diarrhoea, eczema, gout, indigestion, dropsy, fever, impotence, chronic cough, liver disorders, wounds and the common cold (*5, 12*).

Pharmacology

Experimental pharmacology

Antihypercholesterolaemic activity

Intragastric administration of 30.0 g/kg body weight (bw) or 50.0 g/kg bw of an ethanol extract of Semen Trigonella daily for 4 weeks to hypercholesterolaemic rats reduced plasma cholesterol levels by 18% and 25%, respectively. Treatment also lowered liver cholesterol concentrations in these animals (*24*).

Antihyperglycaemic activity

Oral administration of 250.0 mg of an aqueous or methanol extract of seeds daily to normal and diabetic rats significantly reduced blood glucose levels after eating or the administration of glucose ($P < 0.05$) (*25*). Intragastric administration of 250.0 mg of an ethanol extract of the seeds daily for 28 days reduced blood glucose levels in rats with streptozotocin-induced diabetes (*26*), and increased the number of beta cells and the diameter of pancreatic islet cells (*27*).

Intragastric administration of 2.0 g/kg bw or 8.0 g/kg bw of the seeds to rats with or without alloxan-induced diabetes produced a significant decrease ($P < 0.05$) in blood glucose (*28*). Intragastric administration of a single dose of 0.5 ml of a decoction or 200.0 mg/kg bw of an ethanol extract of the seeds to mice with or without alloxan-induced diabetes reduced serum glucose levels (*29*). Chronic administration of a high-fibre defatted extract of the seeds in the diet (content not specified) to dogs with alloxan-induced diabetes for 21 days decreased hyperglycaemia and glucosuria, and reduced the high levels of plasma glucagon and somatostatin (*30*). Intragastric administration of an acetone extract of the seeds (dose not specified) to fasted rats antagonized hyperglycaemia induced by cadmium or alloxan but had no effect on normal animals (*31*).

Anti-implantation activity

Extracts of the seeds (undefined) exhibited anti-implantation effects (approximately 30%) in rats when administered orally in a single dose of 25.0 mg/kg bw from day 1 to day 10 of pregnancy. The average number of fetal implants was significantly decreased ($P < 0.05$) (*32*).

Antioxidant activity
Administration of 2 g/kg bw of the seeds in the diet of rats with alloxan-induced diabetes lowered lipid peroxidation, increased the glutathione and β-carotene concentrations and reduced the α-tocopherol content in the blood (*33*).

Gastrointestinal effects
Administration of 10.0 mg/300 g bw, 12.5 mg/300 g bw or 100.0 mg/300 g bw of a steroid-enriched extract of the seeds per day in the diet to rats with or without streptozotocin-induced diabetes significantly ($P < 0.01$) increased food intake and the motivation to eat. The treatment also decreased total plasma cholesterol without changing the level of triglycerides (*34, 35*).

Toxicology
Intragastric administration of a debitterized powder of the seeds to mice and rats, 2.0 g/kg bw and 5.0 g/kg bw respectively, did not produce any signs of acute toxicity or mortality. In a 90-day subchronic study, weanling rats were fed with the powder in the diet, 1.0%, 5.0% or 10.0%. Terminal autopsy showed no signs of organ damage, increase in liver enzymes, haematological changes or toxicity (*36*).

Administration of a saponin fraction from the seeds by intramuscular injection, by intraperitoneal injection, 50.0 mg/kg bw per day, or in drinking-water, 500.0 mg/kg bw, to chicks for 21 days decreased body weight and increased liver enzymes. Pathological changes observed included fatty cytoplasmic vacuolation in the liver, necrosis of hepatocytes with lymphocytic infiltration, epithelial degeneration of the renal tubules, catarrhal enteritis, myositis and peritonitis (*37*).

Intragastric administration of an aqueous or 95% ethanol extract of the seeds (dose not specified) stimulated uterine contractions in healthy and pregnant rats, mice and guinea-pigs (*38, 39*). In vitro, a 50% ethanol extract of the seeds, 2%, had spermicidal effects and immediately immobilized human sperm on contact (*40, 41*).

Clinical pharmacology

Numerous clinical studies have assessed the effects of the seeds on serum cholesterol and glucose levels in patients with mild to moderate hypercholesterolaemia or diabetes (*18–21, 42*).

In a crossover trial, the effects of a powder of the seeds of *Momordica charantia* (MC) or T*rigonella foenum-graecum* (TF), or a combination of the two on total serum cholesterol, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, very-low-density-lipoprotein

cholesterol and triglycerides were investigated in 20 hypercholesterolaemic non-insulin dependent diabetes mellitus patients. Each subject was given 4.0 mg of MC, 50.0 mg of TF or a 50% combination of the two per day for 14 days. Mean serum total cholesterol was 271.4 mg/dl at the start of the study, and was significantly ($P < 0.001$) decreased to 234.1 mg/dl, 230.6 mg/dl and 225.8 mg/dl after MC, TF or the combination treatment, respectively. All other lipid parameters were also significantly decreased ($P < 0.001$) (*21*).

In a placebo-controlled clinical trial, the effect of ginger and Semen Trigonella on blood lipids, blood sugar, platelet aggregation, and fibrinogen and fibrinolytic activity was investigated. The subjects included healthy volunteers and patients with coronary artery disease and/or insulin-dependent diabetes mellitus. Healthy subjects treated with 2.5 g of the seeds twice per day for 3 months showed no changes in blood lipids and blood sugar (either fasting or after eating). However, in diabetic patients with cardiovascular disease, the treatment significantly ($P < 0.001$) decreased total cholesterol and triglycerides, without affecting high-density-lipoprotein concentrations. In diabetic patients without cardiovascular disease, the seeds reduced blood sugar levels in both fasting and non-fasting subjects, although the treatment was not effective in patients with severe diabetes (*20*).

A prescribed diet with or without the seeds, 25.0 g/day, was given to 60 patients with non-insulin dependent diabetes for a 7-day preliminary period and then for a 24-week trial. The diet containing the seeds lowered fasting blood glucose and improved glucose tolerance. The 24-hour urinary sugar excretion was significantly reduced ($P < 0.001$), and glycosylated haemoglobin was significantly reduced ($P < 0.001$) by week 8 of the trial (*19*).

The effect of the seeds on blood glucose and the serum lipid profile was assessed in 10 patients with insulin-dependent (type I) diabetes patients. Isocaloric diets with or without the seeds, 100.0 g/day, were administered in a randomized manner for 10 days. The diet containing the seeds significantly reduced ($P < 0.001$) fasting blood sugar and improved glucose tolerance tests. There was a 54% reduction in 24-hour urinary glucose excretion. Serum total cholesterol, low-density-lipoprotein cholesterol, very-low-density-lipoprotein cholesterol and triglycerides were also reduced. The high-density-lipoprotein cholesterol concentrations remained unchanged (*18*).

In a long-term study, 60 patients with diabetes ingested 25.0 g of seeds per day for 24 weeks. No changes in body weight or levels of liver enzymes, bilirubin or creatinine were observed, but blood urea levels decreased after 12 weeks. No evidence of renal or hepatic toxicity was observed (*43*).

Adverse reactions

Allergic reactions to the seeds following ingestion or inhalation have been reported (*44, 45*). These reactions range from rhinorrhoea, wheezing, fainting and facial angioedema (*45*). A 5-week-old infant had a 10-minute episode of unconsciousness after drinking a tea prepared from the seeds; however, upon medical examination, all tests were normal (*46*).

Contraindications

Semen Trigonellae Foenugraeci is contraindicated in cases of allergy to the plant material. Owing to its stimulatory effects on the uterus, the seeds should not be used during pregnancy (*39*).

Warnings

No information available.

Precautions

Drug interactions

Owing to its effect on blood glucose levels in diabetic patients, Semen Trigonellae Foenugraeci should only be used in conjunction with oral antihyperglycaemic agents or insulin under the supervision of a health-care professional.

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous and a chloroform/methanol extract of the seeds were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*47*, *48*). The extracts were also not mutagenic in pig kidney cells or in trophoblastic placental cells (*47*).

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried seeds, extracts, fluidextracts and tinctures (*23*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose. Internal use, cut or crushed seed, 6 g, or equivalent of preparations; infusion, 0.5 g of cut seed macerated in 150 ml cold water for 3 hours, several cups; fluidextract 1:1 (g/ml), 6 ml; tincture 1:5 (g/ml), 30 ml; native extract 3–4:1 (w/w), 1.5–2 g. External use: bath additive, 50 g of powdered seed mixed with 250 ml water, added to a hot bath; poultice, semi-solid paste prepared from 50 g of powdered seed per litre of hot water, apply locally (*23*).

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Cortex Uncariae

Definition

Cortex Uncariae consists of the dried stem bark of *Uncaria tomentosa* (Willd.) DC. (Rubiaceae).

Synonyms

Nauclea aculeata auct. Non Willd., *N. cinchoneae* DC, N. polycephala A. Rich., *N. tomentosa* Willd., *Ourouparia polycephala* Baill., *Uncaria surinamensis* Miq., *U. tomentosa* DC, *Uruparia tomentosa* (Willd.) O. Kuntze (*1*, *2*).

Selected vernacular names

Bejuco de agua, cat's claw, cat's thorn, deixa, garabato, garabato amarillo, garabato colorado, garra gavilán, hank's clay, jipotatsa, Katzenkralle, kug kukjaqui, micho-mentis, paotati-mosha, paraguyayo, rangaya, saventaro, toroñ, tsachik, tua juncara, uña de gato, uña de gato de altura, uncucha, unganangi, unganangi, unha de gato (*1–5*).

Geographical distribution

Indigenous to Central America and northern South America including Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Nicaragua, Peru, Suriname, Trinidad and Tobago, and Venezuela, with Peru being the main source (*1*, *6*, *7*).

Description

A scrambling liana, up to 20–30 m long, main stem up to 25 cm in diameter. Branches obtusely quadrangular, generally puberulous. Stipules widely ovate-triangular, minutely and densely puberulous outside. Leaves opposite, petiolate; petioles 1.0–1.5 cm long, minutely puberulous or hirtellous; leaf blades ovate to ovate-oblong, 6.0–14.5 cm long, 2.5–8.5 cm wide; apex obtuse to acuminate; base rounded or subtruncate or subcordate; margin entire or occasionally crenulate in the upper half, glabrous or subglabrous above except strigillose on veins, area between veins densely

puberulent to subglabrous beneath; lateral veins six to ten pairs, level above, prominent beneath, tertiary veins distinct. Spines strongly recurved, tomentose in younger branches, glabrous in older ones. Inflorescences thyrsic with three to nine nodes, lateral units with one to eight pseudo-heads, the bracts reduced; heads small, 12–20 mm in diameter; peduncles densely hirtellous, 1.5–4 cm long. Flowers sessile; calyx tubular, 0.5–0.8 mm long with the obtuse lobes 0.2–0.3 mm long, densely villosulous outside, densely sericeous inside at the base; corolla densely retrorsely adpressed, puberulous outside, glabrous inside, tubes 3.5–5.0 mm long, 0.7–0.8 mm wide at the base, 1.0 mm wide at the mouth, lobes suborbicular, rounded, 1–1.5 mm long, 1–1.5 mm wide. Stamens five, some sterile; anthers 1.0–1.5 mm long, obtuse at the apex, prolonged and attenuated at the base; filaments around 0.2 mm long. Ovary 1.4–1.6 long, 0.9–1.3 mm wide, densely villosulous, style 6.5–9 mm long, glabrous; stigma 1.0 mm long, clavate. Capsules 0.8–1.2 cm long, pubescent outside; seeds with two long narrow wings, one bifid, 3.4 mm long (*6, 8–10*).

Plant material of interest: dried stem bark

General appearance

Shavings or chopped stem bark contain numerous bast fibres up to 7 cm long, fibre bundles and fine-crumbling rind/bark breaking into pieces. The sawdust-like chopped stem bark consists of wood fibres up to 1 cm long with a small fraction of short bast fibres and traces of powdered bark (*4*).

Organoleptic properties

No characteristic odour or taste (*4*).

Microscopic characteristics

Rings dark, partly elevated, but hardly structured. Under illumination, bast fibres show net-like or reticulate structure; with illumination from above, they glimmer with a brownish shimmer. Powdered stem bark consists of finely broken pieces of wood, bast and bark, and clear, crystalline particles of dried sap (*4*).

Powdered plant material

To be established in accordance with national requirements.

General identity tests

Macroscopic and microscopic examinations (*1, 4*), thin-layer chromatography (*4, 11*), and high-performance liquid chromatography for the presence of characteristic oxindole alkaloids (*4, 12, 13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the European pharmacopoeia (*15*) and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

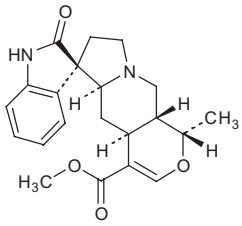
Chemical assays

Not more than 0.02% total tetracyclic oxindole alkaloids determined by high-performance liquid chromatography (*4, 12, 13*).

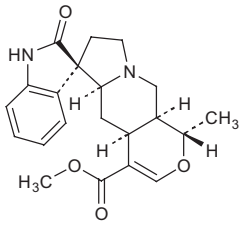
Major chemical constituents

The major constituents are indole alkaloids (0.15–4.60%), primarily pentacyclic oxindoles. The principal pentacyclic oxindole alkaloids are pteropodine, isopteropodine, speciophylline, uncarine F, mitraphylline and isomitraphylline. Tetracyclic oxindoles present include isorhynchophylline and rhynchophylline (*1, 4, 5, 12, 17*). The structures of the major pentacyclic oxindole alkaloids are presented below.

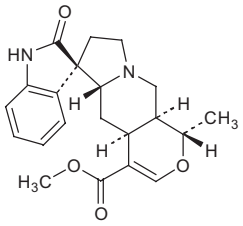
mitraphylline



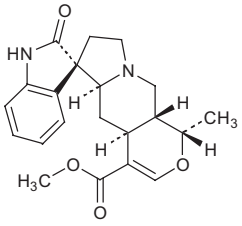
pteropodine



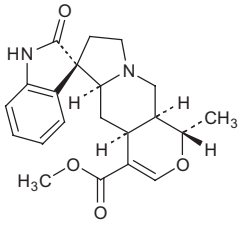
uncarine F



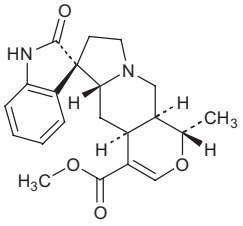
isomitraphylline



isopteropodine



speciophylline



Medicinal uses

Uses supported by clinical data

None. Although two clinical studies have suggested that Cortex Uncariae may be an immunostimulant and increase the number of white blood cells (*18, 19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of arthritis, rheumatism and gastric ulcers (*7, 10, 20*).

Uses described in traditional medicine

Treatment of abscesses, asthma, fevers, urinary tract infections, viral infections and wounds. As an emmenagogue (*4, 5, 21*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

Addition of an undefined extract of the stem bark to the cell medium at a concentration of 100 µg/ml significantly attenuated ($P < 0.05$) peroxynitrite-induced apoptosis in HT29 (epithelial cells) and RAW 264.7 cells (macrophages). The extract further inhibited lipopolysaccharide-induced nitric oxide synthase gene expression (iNOS), nitrite formation, cell death, and the activation of nuclear transcription factor-κβ in RAW 264.7 cells. Oral administration of the extract in drinking-water, 5 mg/ml, attenuated indometacin-enteritis in rodents as evidenced by reduced myeloperoxi-

dase activity, morphometric damage and liver metallothionein expression (*22*).

The anti-inflammatory activities of two types of extracts from the stem bark: a hydroalcoholic extract containing 5.61% alkaloids (mainly of the pentacyclic type, extract A) and an aqueous freeze-dried extract containing 0.26% alkaloids (extract B) were assessed in the carrageenan-induced rat paw oedema test. Extract A was significantly more active than extract B, suggesting that the effect could be due to the presence of pentacyclic oxindole alkaloids. Both extracts showed little inhibitory activity on cyclooxygenase-1 and -2. Only a slight inhibitory activity on DNA-binding of NF-κB was observed (*23*).

The effects of a decoction of the stem bark, 10.0 µg/ml freeze-dried, on tumour necrosis factor-α (TNF-α) production and cytotoxicity in lipopolysaccharide-stimulated murine macrophages (RAW 264.7 cells) was assessed in vitro. The decoction prevented oxidative- and ultraviolet irradiation-induced cytotoxicity. It also suppressed TNF-α production by approximately 65–85% ($P < 0.01$) at concentrations of 1.2–28.0 ng/ml (*24*).

Cinchonain Ib, a procyanidin from the stem bark, inhibited the activity of 5-lipoxygenase, ≥ 100% at 42.5 µmol/ml, indicating an anti-inflammatory effect (*25*).

Antitumour activity

Growth inhibitory activities of an aqueous extract of the stem bark were examined in vitro using two human leukaemic cell lines (K562 and HL60) and one human Epstein–Barr virus-transformed B lymphoma cell line (Raji). Cell proliferation of HL60 and Raji cells was strongly suppressed in the presence of the aqueous extract, while K562 was more resistant to the inhibition. The suppressive effect was mediated through induction of apoptosis, which was shown by characteristic morphological changes, internucleosomal DNA fragmentation after agarose gel electrophoresis and DNA fragmentation quantification. The extract also induced a delayed type of apoptosis becoming most dose-dependently prominent after 48 hours of exposure. Both DNA single- and double-strand breaks were increased 24 hours following treatment (*26*). Leukaemic HL60 and U-937 cells were incubated with pure alkaloids from *U. tomentosa* root. The pentacyclic oxindole alkaloids inhibited the growth, median inhibitory concentration (IC_{50}) 10^{-5}–10^{-4} mol/l; the most pronounced effect was found for uncarine F. Selectivity between leukaemic and normal cells was observed (*13*).

Immune stimulating activity

Addition of 1 µmol/l of pentacyclic oxindole alkaloids (POA) induced endothelial cells to release some as yet to be determined factor(s) into the

supernatant, which enhanced the proliferation of normal human resting or weakly activated B and T lymphocytes. In contrast, proliferation of normal human lymphoblasts and of both the human lymphoblastoid B cell line Raji and the human lymphoblastoid T cell line Jurkat was inhibited, while cell viability was not affected. However, it was shown that the tetracyclic oxindole alkaloids had antagonistic effects to the POA, and dose-dependently reduced the proliferation of lymphocytes stimulated by POA (*27*).

Two commercial extracts of the stem bark, containing approximately 6 mg/g total oxindoles were assessed for the ability to stimulate the production of interleukin-1 (IL-1) and interleukin-6 (IL-6) in alveolar macrophages. A phosphate-buffered saline solution of the extracts stimulated IL-1 and IL-6 production by rat macrophages in a dose-dependent manner in the concentration range 0.025–0.1 mg/ml. In lipopolysaccharide (LPS)-stimulated macrophages, the extracts potentiated the stimulating effects of LPS on IL-1 and IL-6 production indicating an immune stimulating effect (*20*).

The immune effects of an aqueous stem bark extract were assessed after intragastric administration of the extract, 5.0–80.0 mg/kg body weight (bw) per day for 8 consecutive weeks. Phytohaemagglutinin (PHA)-stimulated lymphocyte proliferation was significantly ($P < 0.05$) increased in splenocytes of rats treated at doses of 40.0 mg/kg bw and 80.0 mg/kg bw. White blood cells from the groups treated with 40.0 mg/kg bw and 80.0 mg/kg bw per day for 8 weeks or 160.0 mg/kg bw per day for 4 weeks were significantly elevated ($P < 0.05$) as compared with controls. Repair of DNA single- and double-strand breaks 3 hours after 12 whole body irradiations were also significantly improved ($P < 0.05$) in rats treated with the stem bark (*19*).

Aqueous extracts of the stem bark, depleted of indole alkaloids (< 0.05%, w/w), were assessed for the treatment of chemically-induced leukopenia in rats. The animals were treated first with doxorubicin (DXR), three intraperitoneal injections of 2 mg/kg bw given at 24-hour intervals, to induce leukopenia. Beginning 24 hours after the last DXR treatment, the rats received 80 mg/kg bw of the aqueous extract per day by intragastric administration for 16 days. Animals treated with the extract recovered significantly sooner ($P < 0.05$) than those receiving DXR alone, and all fractions of white blood cells were proportionally increased. The mechanism of action on white blood cells is not known; however, data showing enhanced effects on DNA repair and immune cell proliferative response support a general immune enhancement (*28*).

Intraperitoneal administration of 10.0 mg/kg bw of an oxindole alkaloid-enriched extract of the stem bark enhanced phagocytosis in mice as assessed by the clearance of colloidal carbon. However, the pure alkaloids were not active without the presence of catechins such as the catechin tannin fraction of the root (*29*). In vitro, alkaloids from the stem bark were tested in two chemoluminescence models (granulocyte activation, phagocytosis) for their ability to enhance phagocytotic activity. Isopteropodine showed the strongest activity (55%), followed by pteropodine, isomitraphylline and isorhynchophylline (*29*).

Toxicity

The median lethal and toxic dose of a single oral dose of an aqueous extract of the stem bark in rats was > 8.0 g/kg bw. Although the rats were treated daily with aqueous extracts at doses of 10–80 mg/kg bw for 8 weeks or 160 mg/kg bw for 4 weeks, no symptoms of acute or chronic toxicity were observed. In addition, no changes in body weight, food consumption and organ weight, or kidney, liver, spleen and heart pathological changes were found to be associated with treatment (*19*).

Aqueous extracts of the stem bark were analysed for the presence of toxic compounds in Chinese hamster ovary cells and bacterial cells (*Photobacterium phosphoreum*) in vitro. At concentrations of 10.0–20.0 mg/ml, the extracts were not cytotoxic (*30*).

Clinical pharmacology

Immune stimulating activity

In a human volunteer study, an aqueous extract of the stem bark was administered to four healthy volunteers daily at a dose of 350.0 mg/day for 6 consecutive weeks. No side-effects were reported as judged by haematology, body weight changes, diarrhoea, constipation, headache, nausea, vomiting, rash, oedema or pain. A significant increase ($P < 0.05$) in the number of white blood cells was observed after 6 weeks of treatment (*19*).

Oral administration of two doses of 350 mg of an extract of the stem bark containing 0.05% oxindol alkaloids and 8–10% carboxy alkyl esters per day to human volunteers stimulated the immune system, as evidenced by an elevation in the lymphocyte/neutrophil ratios of peripheral blood and a reduced decay in 12 serotype antibody titre responses to pneumococcal vaccination at 5 months (*18*).

Adverse reactions

No information available.

Contraindications

Owing to its traditional use as an emmenagogue, Cortex Uncariae is contraindicated during pregnancy.

Warnings

No information available.

Precautions

Drug interactions

Commercial extracts of the stem bark inhibited the activity of human cytochrome P450, $IC_{50} < 1\%$. Cortex Uncariae should only be taken in conjunction with prescription drugs metabolized via cytochrome P450, such as protease inhibitors, warfarin, estrogens and theophylline under the supervision of a health-care provider (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

No information available.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of safety data, the use of Cortex Uncariae during nursing is not recommended, unless under the supervision of a health-care provider.

Paediatric use

Owing to the lack of safety data, the use of Cortex Uncariae in children under the age of 12 years is not recommended, unless under the supervision of a health-care provider.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; and teratogenic effects in pregnancy.

Dosage forms

Dried stem bark for infusions and decoctions, and extracts. Capsules and tablets. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: extracts, 20.0–350.0 mg (*10, 19*). Capsules and tablets: 300.0–500.0 mg, one capsule or tablet two to three times.

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Fructus Zizyphi

Definition

Fructus Zizyphi consists of the dried ripe fruits of *Zizyphus jujuba* Mill. (*1*)[1] or *Z. jujuba* var. *inermis* Rehd. (Rhamnaceae) (*1–5*).

Synonyms

Rhamnus ziziphus L., *Zizyphus mauritiana* Lam., *Z. sativa* Gaertn., *Z. vulgaris* Lam., *Z. vulgaris* Lam. var. *inermis* Bunge, *Z. zizyphi* Karst. (*5–8*).

Selected vernacular names

Annab, badari, bayear, ber, black date, bor, borakoli, borehannu, brustbeeren, Chinese date, Chinese jujube, common jujube, da t'sao, desi ber, hei zao, hong zao, ilandai, jujube, jujube date, jujube plum, kamkamber, koli, kul, kul vadar, lanta, lantakkura, narkolikul, natsume, onnab, phud sa chin, red date, regi, spine date, unnab, vadai, vadar, vagari, zao (*1–3, 5–12*).

Geographical distribution

Indigenous over a wide area, from Southern Europe to South-East and East Asia. Cultivated in China, India, Japan and Republic of Korea (*5, 9–11*).

Description

A spiny, deciduous shrub or a small tree, up to 10 m high; spines in groups of two, one straight, up to 2.5 cm long and one curved. Leaves alternate, petiolate, oval-lanceolate, 2–7 cm long, 2.5–3.0 cm wide; apex slightly obtuse; base oblique; margin closely serrulate, with three veins. Inflorescence an axillary cyme. Flowers perfect, seven to eight in each cluster; calyx with cupuliform tube and five segments; petals five, yellow; disk lining the calyx tube; stamens five; ovary depressed into the disk. Fruits

[1] Included in the *Pharmacopoeia of the People's Republic of China* (*1*) as Fructus Jujubae.

are fleshy drupes, ovoid or oblong, 1.5–5.0 cm long, dark reddish brown when ripe (*7, 9, 10*).

Plant material of interest: dried ripe fruits

General appearance

Ellipsoidal or broad ovoid, 2–3 cm long, 1–2 cm in diameter; externally reddish brown with coarse wrinkles, or dark greyish red with fine wrinkles, lustrous; both ends slightly dented, with a scar of style at one end and a scar of peduncle at the other; epicarp thin and leathery; mesocarp thick, dark greyish brown, spongy, soft and adhesive; endocarp extremely hard, fusiform and divided into two loculi; seeds flat and ovoid (*1, 3, 4*).

Organoleptic properties

Odour: slightly aromatic; taste: sweet (*1, 3, 4*).

Microscopic characteristics

To be established according to national requirements.

Powdered plant material

To be established according to national requirements.

General identity tests

Macroscopic examination (*1, 3, 4*) and thin-layer chromatography (*1, 5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 1.0% (*5*).

Total ash

Not more than 2.0% (*1*).

Acid-insoluble ash

Not more than 4.0% (*4*).

Water-soluble extractive

Not less than 17.0% (*4*).

Alcohol-insoluble extractive
Not less than 19.0% (*4*).

Loss on drying
Not more than 10.0% (*4*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

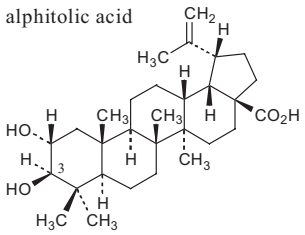
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

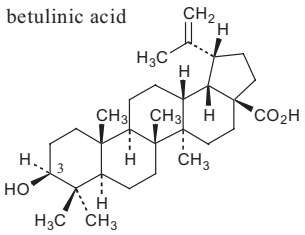
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

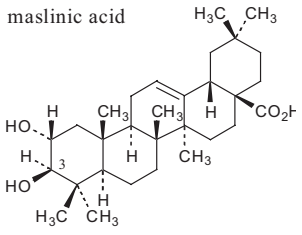
Other purity tests
Chemical tests to be established in accordance with national requirements.

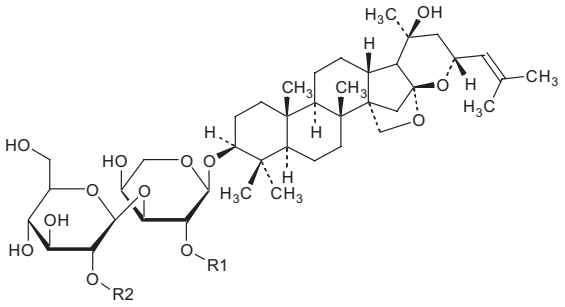
Chemical assays
Qualitative and quantitative high-performance liquid chromatography for the presence of 3-*O*-*trans*- and 3-*O*-*cis*-*p*-coumaroylalphitolic acid (*16*), and jujubosides A and B (*17*).

Major chemical constituents
Major characteristic constituents are triterpenes and triterpene saponins, including alphitolic, betulinic, maslinic, oleanolic, ursolic, 3-*O*-*trans*-alphitolic, 3-*O*-*cis*-*p*-alphitolic alphitolic, 3-*O*-*cis*-*p*-coumaroylalphitolic, and 3-*O*-*trans*-*p*-coumaroylalphitolic acids; and zizyphus saponins I, II, III, jujuboside B, spinosin and swertisin (*12, 18–22*). Three triterpene oligoglycosides, jujubosides A1 and C, and acetyljujuboside B have been isolated from the seeds (*23, 24*). Also present in the fruit are the biologically active compounds cyclic AMP and cyclic GMP (*25*), with concentrations estimated at 100–500.0 nmol/g and 30–50.0 nmol/g, respectively (*26*). A polysaccharide named ziziphus-arabinan has also been isolated from the fruit (*27*). The structures of representative triterpene and saponins are presented below.

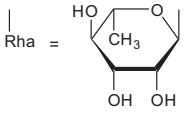




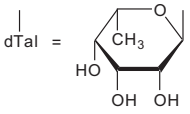




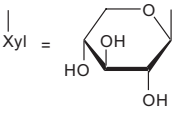
	R1	R2
jujuboside B	Rha	Xyl
zizyphus saponin I	dTal	H
zizyphus saponin II	Rha	H
zizyphus saponin III	dTal	Xyl



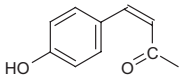
6-deoxy-α-L-mannopyranosyl

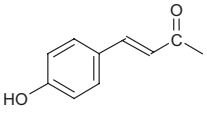


6-deoxy-α-L-talopyranosyl



β-D-xylopyranosyl

cis-p-coumaroyl 

trans-p-coumaroyl 

Medicinal uses

Uses supported by clinical data

None. Although one uncontrolled human study has suggested that Fructus Zizyphi may be of some benefit for the treatment of insomnia (*28*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

To promote weight gain, improve muscular strength, and as an immunostimulant to increase physical stamina. Treatment of insomnia due to irritability and restlessness (*1*).

Uses described in traditional medicine

As an antipyretic, diuretic, emmenagogue, expectorant, sedative and tonic. Treatment of asthma, bronchitis, diabetes, eye diseases, inflammatory skin conditions, liver disorders, scabies, ulcers and wounds (*12, 29*).

Pharmacology

Experimental pharmacology

Antiallergenic activity

Intraperitoneal injection of 100.0 mg/kg body weight (bw) of a 100% ethanol extract of the Fructus Zizyphi or the active constituent of the ethanol extract, ethyl α-D-fructofuranoside, daily for 5 days, inhibited haemagglutination-induced anaphylaxis in rats (*30*). A saline extract (0.85% sodium chloride) of the fruits (concentration not specified) prevented hypotonic and heat stress-induced haemolysis of erythrocyte membranes in vitro (*31*). Three triterpene oligoglycosides, jujubosides A1 and C, and acetyljujuboside B, in varying concentrations inhibited histamine release from rat peritoneal exudate cells induced by antigen–antibody reaction (*23*).

Anti-inflammatory activity

A methanol extract of the fruits, 0.1 mg/ml, did not suppress interleukin-8 induction in lipopolysaccharide-activated rat macrophages in vitro (*32*). A polysaccharide isolated from an aqueous extract of the fruits, Ziziphus-arabinan, 500.0 µg/ml, had anti-complementary activity in human serum in vitro (*27*). Both the *n*-butanol and diethyl ether extracts of the seeds exhibited anti-inflammatory activity in vitro as assessed by the albumin-stabilizing assay (*33*).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats daily for 4 days, produced a significant inhibition of carrageenan-induced footpad oedema (50.0% reduction, $P < 0.05$), and cotton pellet-induced granulomas (25.0% reduction, $P < 0.05$) (*29*).

Analgesic activity

A hot aqueous extract of the fruits did not inhibit conduction in the frog sciatic nerve when added to the bath medium at a concentration of 2.0% (*34*). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to mice reduced the responsiveness of mice in the hot-plate and tail-flick tests, thereby demonstrating analgesic effects (*29*).

Antihyperglycaemic activity

Intragastric administration of a single dose of 1.0 g/kg bw of a 95% ethanol extract of the dried seeds suspended in water lowered the mean blood glucose concentrations in rabbits with alloxan-induced diabetes (*35*).

CNS depressant activity and toxicity

Chronic administration of 100.0 mg/kg bw of a 95% ethanol extract of the fruits to mice in drinking-water daily for 3 months had no effects on mortality, haematology, organ weight or sperm production (*29*). Intragas-

tric administration of an aqueous extract of the fruits, three doses of 0.5 mg/kg bw, 1.0 mg/kg bw or 3.0 mg/kg bw over 24 hours, to mice had no acute toxic effects (*29*). Intragastric administration of a 95% ethanol extract of the fruits, three doses of 1.0 g/kg bw over 24 hours, had no acute toxic effects. However, sedation was noted in animals treated with three doses of 3.0 g/kg bw (*29*).

Subcutaneous administration of 500.0 mg/kg bw of an aqueous extract of the seeds daily to mice depressed central nervous system activity, as measured by the potentiation of hexobarbital-induced sleeping time and antagonism of caffeine-induced hyperactivity (*36*). However, intraperitoneal administration of 500.0 mg/kg bw of a 75% methanol extract of the seeds to mice failed to have any effect on barbiturate-induced sleeping time (*37*). A saponin fraction of a defatted seed extract potentiated barbiturate-induced sleeping time when administered by intraperitoneal injection, 50.0 mg/kg bw (*38, 39*). Intraperitoneal and intragastric administration of up to 1.0 g/kg of a butanol, methanol or alkaloid-enriched fraction of a methanol extract of the fruits had tranquillizing effects in mice (*37, 40*). Intraperitoneal administration of 500.0 mg/kg bw of the flavonoids spinosin and swertisin, isolated from a petroleum ether extract of the dried seeds, had mild CNS-depressant effects in mice and potentiated hexobarbital-induced sleeping time by 50% (*39*).

An aqueous extract of the fruits, 100.0 mg/kg bw per day, administered to mice in the drinking-water for 3 months reduced average weight gain when compared with the controls (no extract). Two mice developed alopecia of the snout, one was anaemic and one was suffering from protrusion of the penis (*29*). The mortality rate compared to control animals was not significantly different, and there were no significant haematological changes ($P > 0.05$). Intragastric administration of 50.0 g/kg bw of a decoction of the fruits to mice had no toxic effects (*41*). No deaths occurred in mice given an aqueous extract of the fruits (15 g). The intraperitoneal median lethal dose (LD_{50}) of the decoction was 14.3 g/kg bw in rats. Subcutaneous administration of 10–15.0 g/kg bw of a 50% ethanol extract of the seeds to mice killed all animals within 30–60 minutes (*41*).

Immune stimulation

A purified polysaccharide, 0.5 mg/ml, isolated from an aqueous extract of the fruits, had anti-complement activity in human serum in vitro (*27*). Intragastric administration of 1.0 g/kg bw of a polysaccharide-enriched fraction from an aqueous extract of the fruits to mice enhanced the activity of natural killer cells (*42*).

Platelet aggregation inhibition
A hexane and 90% methanol extract of the dried seeds, 5.0 mg/ml, inhibited collagen-induced platelet aggregation in vitro (*43*).

Clinical pharmacology
Fructus Zizyphi is often a constituent in multicomponent prescriptions used in Kampo and traditional Chinese medicine. Numerous clinical trials have assessed the effects of the fruits in combination with other medicinal plants for anticonvulsant effects, memory-enhancing effects and anti-inflammatory effects. However, a review of these trials is beyond the scope of this monograph, and is therefore not included.

In one uncontrolled study, oral administration of the dried seeds to human subjects produced CNS depressant effects, and was reported to be effective for the treatment of insomnia at a dose of 0.8 g/day (*28*). No further details of this study are available.

Adverse reactions
No information available.

Contraindications
No information available.

Warnings
No information available.

Precautions
Carcinogenesis, mutagenesis, impairment of fertility
An aqueous and a methanol extract of the fruits were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 or the *Bacillus subtilis* recombination assay at concentrations up to 100.0 mg/ml (*44*). A 70% ethanol extract of the fruits, up to 4.0 mg/ml, was not mutagenic in either the SOS-chromotest (*Escherichia coli* PQ37) or the SOS-umu test (*Salmonella typhimurium* TA1535) (*41*).

Intragastric administration of 1.0 g of the fruits per day to rats for 15 months inhibited the growth of adenocarcinomas of the stomach induced by *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (*45*). Administration of a 95% ethanol extract of the fruits in drinking-water, average daily dose 100 mg/kg bw, to mice for 3 months had no significant spermatotoxic effects (*29*).

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried fruits, aqueous and hydroalcoholic extracts. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Daily dose: fruits 6–15 g (*1*).

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Annex 1

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* It was a great sorrow to learn of the death of Professor Fitak in February 2002. He had been working with Traditional Medicine, WHO, Geneva and supporting its projects for many years, especially the development of Volumes 1–3 of the ***WHO monographs on selected medicinal plants***. His great contributions to WHO's work will always be remembered.

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Annex 2

Cumulative index

(in alphabetical order of plant name)

For the convenience of users of Volume 3, the monographs described in Volumes 1 and 2 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume in which the indexed item is to be found. Monographs are listed in alphabetical order of the plant name.

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(in alphabetical order of plant material of interest)

For the convenience of users of Volume 3, the monographs described in Volumes 1 and 2 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume number in which the indexed item is to be found. Monographs are listed in alphabetical order of the plant material of interest.

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